Chapter 1

Clinical Approach in Soft Tissue Tumors

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1.1 EPIDEMIOLOGY

Sarcomas are rare malignant tumors that originate from mesenchymal tissue at any body site. Soft tissue sarcomas comprise approximately 1% of malignant tumors [1,2]. There are more than 50 subtypes, pleomorphic sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor accounting for 75% of the cases. Roughly speaking, 80% of sarcomas originate from soft tissues, whereas the remainder are from bones. More than 10,000 new cases are diagnosed each year in the United States [1,2]. They account for 0.72% of all cancers diagnosed annually, whereas they represent 7% of all cancers in children. In Europe, similar data are reported with almost 8% of neoplasms in children, and almost half of them being less than 5 years of age at diagnosis [3]. Between 1988 and 1997, the age-standardized incidence of soft tissue sarcomas in Europe was 9.1 per million children, with a lower range of affected patients in the western and eastern parts of the continent and a higher one in the northern. The annual incidence is 30 per million [3].

Most soft tissue sarcomas occur in adults older than 55 years. Approximately 50% of bone sarcomas and 20% of soft tissue sarcomas are diagnosed in people younger than 35 years. The gastrointestinal stromal tumor (GIST), the frequency of which has been underestimated, is the most common form of soft tissue neoplasm. Its incidence, prevalence, and clinical aggressiveness also have been underestimated [4]. More recent experience from epidemiologic studies and active GIST therapeutic trials suggest that the annual incidence of GIST in the United States is at least 4000 to 6000 new cases (roughly 7 to 20 cases per million population per year) [4]. Some sarcomas,

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such as leiomyosarcoma, chondrosarcoma, and GIST are more common in adults than in children. Only approximately 500 thigh liposarcomas are diagnosed per year in the United States compared with more than 212,900 adenocarcinomas of the female breast. Thus, the number of adenocarcinomas originating in one anatomic site in women exceeds by almost 500-fold the number of thigh liposarcomas and is 22-fold higher than the total number of soft tissue sarcomas of all pathological varieties, at all anatomical sites, in all age groups, and in both genders.

Most high-grade bone sarcomas, including Ewing sarcoma/peripheral neuroectodermal tumor and osteosarcoma, are much more common in children and young adults. Among children, soft tissue sarcomas are two times more common in Caucasians than in African Americans. Rhabdomyosarcoma is the most frequent childhood soft tissue sarcoma (50%). Population-based data from Connecticut covering the years 1935–1989 have shown an increased incidence of soft tissue sarcomas in both genders, with men being more affected than women. The recent increase of acquired immune deficiency syndrome–related Kaposi sarcoma does not explain the upward trend in soft tissue sarcoma, dating back decades. A similar trend was found in a population-based study including 5802 cases of soft tissue sarcomas in children aged 0–14 years, which was extracted from the database of the Automated Childhood Cancer Information System (ACCIS) and registered in population-based cancer registries in Europe for the period 1978–1997. The incidence of soft tissue sarcomas in children increased by almost 2% per year during the period 1978–1997 as a result of the higher incidence of genitourinary rhabdomyosarcoma [3]. In most cases of soft tissue sarcomas, precise etiology is unknown, although several associated or predisposing factors have been identified, including environmental, physical, biological, and chemical factors.

1.1.1 Previous Local Injury

Soft tissue sarcomas can develop in areas of scar tissue after surgery, burns, fractures, radiation therapy [5–10], chronic irritation, and lymphedema out. The number of cancer patients who live longer after a curative treatment of a primary neoplasm is increasing. Therefore, childhood cancer survivors have an increased risk for developing secondary sarcomas. Postirradiation sarcoma, although uncommon, is more frequent because the number of long-term survivors increases [5]. The risk of subsequent bone cancer among 9170 patients who had survived 2 or more years after the diagnosis of a cancer in childhood has been estimated [6]. As compared with the general population, the patients had a relative risk of 133 (95% confidence interval [CI], 98–176) and a mean ± (standard error [SE]) 20-year cumulative risk of 2.8 ± 0.7% [6]. A large cohort of childhood cancer survivors was followed to determine the true incidence of secondary sarcomas. The history of secondary sarcomas in 14,372 participants in the Childhood Cancer Survivor Study was determined from self-reports in three questionnaires [7]. A total of 108 patients developed sarcomas in a median of 11 years after the initial diagnosis of childhood cancer. The risk of sarcoma was more than nine-fold higher among childhood cancer survivors than among the general population (standardized incidence ratio [SIR] = 9.02, 95% CI = 7.44–10.93). The excess absolute risk of secondary sarcoma was 32.5 per 100,000 person-years (95% CI = 26.1–40.3 per 100,000 person-years). Higher standardized incidence ratios and excess absolute risks were associated with a

young age at primary diagnosis, a primary sarcoma diagnosis, and a family history of cancer. In a multivariable model, an increased risk of secondary sarcoma was associated with radiation therapy (relative risk [RR] = 3.1, 95% CI = 1.5–6.2), a primary diagnosis of sarcoma (RR = 10.1, 95% CI = 4.7–21.8), a history of other secondary neoplasms (RR = 2.2, 95% CI = 1.1–4.5), and treatment with higher doses of anthracyclines (RR = 2.3, 95% CI = 1.2–4.3) or alkylating agents (RR = 2.2, 95% CI = 1.1–4.6) [6]. A study attempted to evaluate the risk of soft tissue sarcoma in areas close to previously irradiated anatomic regions in women with breast carcinoma. This population-based, retrospective cohort study allowed identifying 194,798 women who were diagnosed with invasive breast carcinoma between 1973 and 1995. According to data from the Surveillance, Epidemiology and End Results Program (SEER), 54 women in the radiation therapy cohort and 81 women in the nonradiation therapy cohort subsequently developed soft tissue sarcomas. In the radiation therapy cohort, the age-standardized incidence ratios were 26.2 (95% CI=16.5–41.4) for angiosarcoma and 2.5 (95% CI=1.8–3.5) for other sarcomas. In the nonradiation therapy cohort, the age-standardized incidence ratios were 2.1 (95% CI=1.0–4.4) and 1.3 (95% CI=1.0–1.7), respectively. The radiation therapy cohort demonstrated a greater risk for developing both angiosarcoma (RR=15.9, 95% CI=6.6–38.1) (Fig 1.1) and other sarcomas (RR=2.2, 95% CI=1.4–3.3) compared with the nonradiation therapy cohort, and the largest increase was observed in the chest wall/breast. The elevated RR was significant even within 5 years of radiation therapy but reached a maximum between 5 and 10 years. That study also showed that the risk of developing soft tissue sarcoma, especially angiosarcoma, was elevated after radiation therapy in women with breast carcinoma [8]. Eighty patients had a confirmed histologic diagnosis of sarcoma that occurred after radiation therapy during 1975 and 1995. The patients were treated for breast cancer (n = 33, 42%), non-Hodgkin lymphoma (n = 9, 11%), cervical cancer (n = 9, 11%), benign lesions (n = 4, 5%), or other tumors (n = 25, 31%). Sarcoma occurred after a mean latency of 12 years (range, 3–64 years), with most (70%) developing in the soft tissues [9]. In another study, the median dose of radiation delivered to the primary tumor site was 45 Gy, and the median interval between radiotherapy and a diagnosis of sarcoma was 14 years. Seven tumors were located in the anatomical region of the sternum, three were located on the lateral chest wall, and five were located in the thoracic outlet [10].

1.1.2 Exposure to Chemicals

The risk of developing a soft tissue sarcoma increases in patients who have been exposed to carcinogenic agents, particularly polycyclic hydrocarbons, asbestos, dioxin, and vinyl chloride [11–16]. The strongest documented association is related to vinyl chloride. In a case-control study of childhood rhabdomyosarcoma, families of 33 cases and 99 controls were interviewed. An RR of 3.9 was associated with fathers' (but not mothers') cigarette smoking (p = .003). For other cases, children had fewer immunizations than controls, particularly smallpox vaccinations (RR = 0.2; p = .001), and conversely had more preventive infections. An RR of 3.2 (p = .03) was found with exposure to chemicals, as well as with diets including giblets meats (RR of 3.7; p = .004). Mothers of affected children older than 30 years of age at the subject's birth, those to be overaged at childbirth, and the role of antibiotics treatment preceding or

during pregnancy also have been assessed. Other findings suggest that low socioeconomic status could be associated with an increased risk of rhabdomyosarcoma. All these findings suggest that environmental factors could play an important role in the etiology of childhood rhabdomyosarcoma [11]. Marijuana and cocaine addiction of parents during the year preceding their child's birth has been reported to increase by two-fold to five-fold the risk of rhabdomyosarcoma in their children [12]. Exposure to phenoxyacetic acids has been associated with a roughly three-fold increased risk for soft tissue sarcoma, therefore confirming previous findings, whereas exposure to chlorophenols was not associated with a risk of developing soft tissue sarcomas in this study [13]. The potential role of phenoxy herbicides and chlorophenols in the development of soft tissue sarcomas also has been evaluated. In studies based on population referents, increased risks for soft tissue sarcoma were documented in gardeners (odds ratio [OR] = 4.1), railroad workers (OR = 3.1), as well as construction workers exposed to impregnating agents (OR = 2.3) [14]. Moreover, it also has been demonstrated [15] that soft tissue sarcoma risk, modeled using conditional logistic regression, was associated significantly with high-intensity chlorophenol exposure (OR = 1.79, 95% CI 1.10–2.88). A duration-response trend was evident among more highly exposed subjects ($p < .0001$). For subjects with 10 or more years of substantial exposure, the odds ratio was 7.78 (95% CI 2.46–24.65). These results suggest that chlorophenol exposure, independent of phenoxyherbicides, may increase the risk of soft tissue sarcoma [16].

1.1.3 Diseases or Conditions

Patients with weakened immune defenses such as human immunodeficiency virus (HIV) infection, congenital (inborn) immune deficiency, or immunosuppressive therapy are at risk for developing soft tissue sarcomas. Kaposi sarcoma is linked to HIV infection. HIV and human herpesvirus 8 has been implicated in the pathogenesis of Kaposi sarcoma. Rare familial syndromes with soft tissue sarcomas sarcoma have been identified. A report from the Cancer Family Registry of the National Cancer Institute allowed retrieving 24 kindreds of a syndrome that includes sarcoma, breast carcinoma, and other neoplasms in young patients. Cancer developed in an autosomal dominant pattern in 151 blood relatives, 119 (79%) of whom were affected before 45 years of age. These young patients had 50 bone and soft tissue sarcomas of diverse histological subtypes and 28 breast cancers. Additional features of the syndrome included an increased incidence of brain tumor (14 cases), leukemia (9 cases), and adrenocortical carcinoma (4 cases) before 45 years of age. These neoplasms also accounted for 73% of the multiple primary cancers occurring in 15 family members. This description led to the discovery of the Li-Fraumeni syndrome, which is related to p53 germline mutations [17,18]. New germline mutations of the p53 gene are rare among patients with "sporadic" sarcoma, whereas they are more frequent in patients whose background includes either multiple primary cancers or a family history of cancer [17]. As many as 7% of children with soft tissue sarcomas have Li-Fraumeni syndrome. The p53 gene seems altered in at least one third of sarcoma patients. In another third of patients, the *MDM2* gene is amplified, resulting in an inhibition of the p53. Soft tissue sarcomas are more frequent among patients with certain inherited conditions including retinoblastoma [19], Li-Fraumeni syndrome, Gardners's syndrome, Werner's syndrome, nevoid basal cell carcinoma

syndrome, neurofibromatosis type 1, and some immunodeficiency syndromes. Indeed, these risk factors account for a minority of soft tissue sarcomas, hence, the need for more genetic and environmental investigations.

1.2 CLINICS AND CLINICAL PROFILES

In day-to-day practice, the suspicion/diagnosis of a soft tissue sarcoma is unusual because of the rarity of these neoplasms; most patients seeking medical advice for a soft tissue lump do have a benign neoplastic or non-neoplastic condition. Some clinical presentations should suggest a reference to a specialist (those with a mass larger than 5 cm, as well as pain, increased size, deep to fascia, or a recurrent mass after previous excision). The definitive tests for diagnosing sarcoma are imaging (ultrasound, X-rays, computed tomography [CT] scan, or magnetic resonance imaging [MRI] scan) and a biopsy. It is important that both imaging and biopsy samples should be performed by experienced radiologists and pathologists in the management of soft tissue lesions. Many benign lumps simulate sarcomas, and they are obviously much more frequent. The contribution of pathologists to the multidisciplinary team of sarcomas, management and in the quality control of sarcoma diagnosis is mandatory. The planning of the surgical procedure follows the histological diagnosis. However, some sarcomas will come to be revealed or diagnosed in unexpected situations (e.g., uterine sarcoma in specimens of hysterectomy or GIST in resected abdominal and gastrointestinal masses). Otherwise, surgery should be undertaken under the supervision of a sarcoma specialist multidisciplinary team, even when the surgeon is not a regular member of that team.

1.2.1 Natural History of Soft Tissue Sarcomas

Soft tissue sarcomas can affect any part of the body. The most frequent location is the lower limb, accounting for about half of the cases, although the abdominal space and the retroperitoneum also are affected. Ideally, a definitive diagnosis should be stated in terms of benignancy or malignancy before any other procedure takes place. An initial surgical removal/biopsy is not recommended to avoid the contamination of the tumor bed, particularly for those lumps suspicious of malignancy. It has been demonstrated that the adequacy of an initial surgical resection was an important factor of prognosis, either in terms of recurrence and/or metastasis. Histologic evaluation of the surgical margins is mandatory [20] for both high- and low-grade neoplasms, whether superficial or deep. Approximately 50% of sarcoma patients will suffer a local recurrence and/or metastasis. For most histologic subtypes of soft tissue sarcomas, the most predictive factor of distant metastatic disease is tumor grade [21, 22]. The metastatic potential of low-grade sarcomas is 5–10%, of intermediate-grade sarcomas is 25–30%, and of high-grade sarcomas is approximately 50–60%. Additional histologic features have been used to evaluate tumor grade such as necrosis, pleomorphism, and the number of mitoses per microscopic high power field (HPF). However, some soft tissue sarcomas do not respond to the usual grading criteria; for example, tumors of the Ewing sarcoma/peripheral neuroectodermal tumor family are all high-grade sarcomas, whereas alveolar soft part sarcoma and some well-differentiated synovial sarcomas, although depicting a

very low mitotic index and a well-recognized tumor type, are unpredictable in their biologic behavior.

Soft tissue sarcomas of the extremities usually metastasize to the lungs (70% of patients), with liver metastases being rare (<5%). Retroperitoneal and organ-based soft tissue sarcomas have a greater incidence of liver metastases with a similar rate of frequency to lung metastases. Myxoid liposarcoma is an exception, with a tendency to metastasize to other sites rather than to the lungs. Lymph node metastases are rare in soft tissue sarcomas and occur in less than 2–3% of cases, with the exception of synovial sarcoma, epithelioid sarcoma, and clear cell sarcoma of tendon sheath whose incidence of lymph node metastases reaches 20% [23].

Several low-grade soft tissue sarcomas are prone to gain a second clone of neoplastic cells during the course of their progression. These so-called "dedifferentiated sarcomas" depict a different phenotype of variable malignancy and can pursue a more aggressive clinical course [24–28]. In terms of oncogenesis, dedifferentiation is a phenomenon of tumor progression that seems to be time dependent. Dedifferentiation occurs in roughly 10% of well-differentiated liposarcomas of any subtype [25–28]. The risk of dedifferentiation is greater for deep-seated (particularly retroperitoneum) tumors and is significantly less for the limbs. Approximately 90% develop de novo, whereas 10% occur in recurrences. Dedifferentiation to leiomyosarcoma or rhabdomyosarcoma or less-differentiated liposarcoma is predictive of a worse prognosis in terms of recurrences, metastases, and survival. The use of microarray technology to evaluate gene expression profiles in biopsy or surgical specimens will provide newer insights into the pathogenesis of these tumors and therefore allow more precise subclassification and optimize the selection of therapeutic targets [8].

1.2.2 Age at Diagnosis

The age of the patient at the first presentation of a soft tissue tumor could be suggestive of a given type of neoplasm. Rhabdomyosarcoma is the most common soft tissue tumor of childhood and accounts for approximately one half of all soft tissue sarcomas in this age group. Approximately 65% of cases occur in children less than 6 years of age. It is less frequent during the early-to-mid teenage years and is rare in adulthood. The two most common subtypes, embryonal and alveolar, account for at least 80% of all rhabdomyosarcomas. Synovial sarcoma is at the crossroads between the pediatric and the adult age groups. Although children and adults with synovial sarcoma share a similar clinical presentation, their outcome differs, which suggests that factors other than unfavorable clinical features could influence their biological behavior. Whether this difference is related to biological variables or to historically different treatment approaches for pediatric versus adult patients is a matter of debate [29]. In adults, 40% of sarcomas are malignant fibrous histiocytomas and 25% are liposarcomas. Fibrosarcoma incidence peaks at ages 30–39 years (24%), whereas leiomyosarcoma peaks later at ages 50–59 years (25%). Malignant fibrous histiocytoma peaks at ages 60–69 years (21%) with a regular increase in incidence between 30 and 70. Liposarcoma also peaks at ages 60–69 years (22.5%), but a high prevalence of liposarcoma is observed from ages 40 to 80 years. Well-differentiated liposarcoma represents the largest subgroup of malignant adipocytic neoplasms and accounts for about 40–45% of all liposarcomas. It occurs in middle-aged adults with a peak incidence in the sixth

decade. Myxoid liposarcoma is a disease of young adults, with a peak incidence in the fourth and fifth decades of life. Although rare, it is the most common form of liposarcoma in patients younger than 20 years old. There is no sex predilection. Most pleomorphic liposarcoma develops in elderly patients (>50 years) with an equal sex distribution.

1.2.3 Tumor Location and Clinical Presentation

Approximately 60% of soft tissue sarcomas develop in the arms and legs, 30% develop in the trunk of the body, and 10% develop in the head and neck.

Rhabdomyosarcomas typically originate in the head and neck region, urinary tract and reproductive organs, as well as the arms and legs. Embryonal rhabdomyosarcoma is generally a localized tumor, with a favorable response to treatment, and it usually gives distant metastases years after the initial diagnosis. When not occurring in the limbs, rhabdomyosarcomas are revealed under different clinical presentation, with a painless lump in the head or neck and symptoms related to the tumor location (e.g., a bulging or a swollen eyelid and even paralysis of the eye muscles, a stuffy or blocked nose, sometimes together with a nasal discharge that contains pus or blood if the sinus is involved with the tumor, and erosion of the skull bones triggering headache and nausea as the tumor gradually grows toward the brain's surface). In the urogenital tract, symptoms and clinical signs such as dysuria, hematuria, the presence of a lump or mass in the vagina, vaginal discharge of blood and mucus, and painless enlargement of the scrotum when the testicle is affected are common.

Synovial sarcomas mostly occur in the vicinity of large joints such as the knees or ankles, although they can originate in other sites, (Fig 1.1). Rare cases of synovial sarcomas of the gastrointestinal tract have been reported, with most of them in the

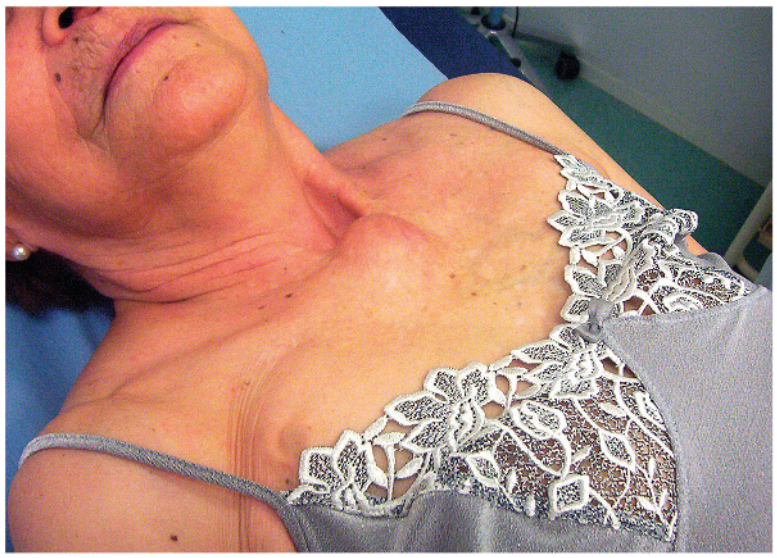

FIG. 1.1 Presternal synovial sarcoma.

esophagus [30]. Synovial sarcomas account for 8–10% of all soft tissue sarcomas. They are characterized by a significant risk for local recurrence, even after a complete surgical excision of a paradoxically well-limited and slowly growing neoplasm. They develop in the vicinity or close to anatomical sites of joints, mostly in the lower limbs (2/3). In a series of 41 patients with synovial sarcoma, a multivariate analysis showed that metastasis at presentation and monophasic tumor subtype affected overall survival. For progression-free survival, monophasic subtype was only one prognostic factor. The study confirmed that histologic subtype is the most important independent prognostic factor of synovial sarcoma regardless of tumor stage [31]. Three histologic subtypes of synovial sarcoma are recognized—biphasic, monophasic, and poorly differentiated tumors. The detection of the characteristic chimeric transcript often contributes to the precision of the histopathological diagnosis, especially when the tumors originate in unusual locations and for the monophasic and poorly differentiated varieties. Previous studies have shown that SYT-SSX1 is the most common SYT-SSX fusion transcript in biphasic synovial sarcomas of the limbs. The detection of a SYT-SSX2 chimeric transcript was confirmed by reverse transcript polymerase chain reaction (RT-PCR) and direct sequencing analysis in both cases. Additional genetic analysis is needed to understand fully the biological and clinical features of synovial sarcoma originating in the thorax [32].

Liposarcomas are mostly neoplasms of the retroperitoneum and the thigh. Well-differentiated liposarcoma occurs most frequently in deep soft tissue of the limbs, especially the thigh (Fig 1.2), followed by the retroperitoneum, the paratesticular area, and the mediastinum. They also can originate in subcutaneous tissues and, very rarely, in the skin (Fig 1.3). The retroperitoneum is the most common anatomic location, outnumbering the soft tissue of extremities by at least 3:1. Other locations include the spermatic cord and, more rarely, the head and neck as well as the

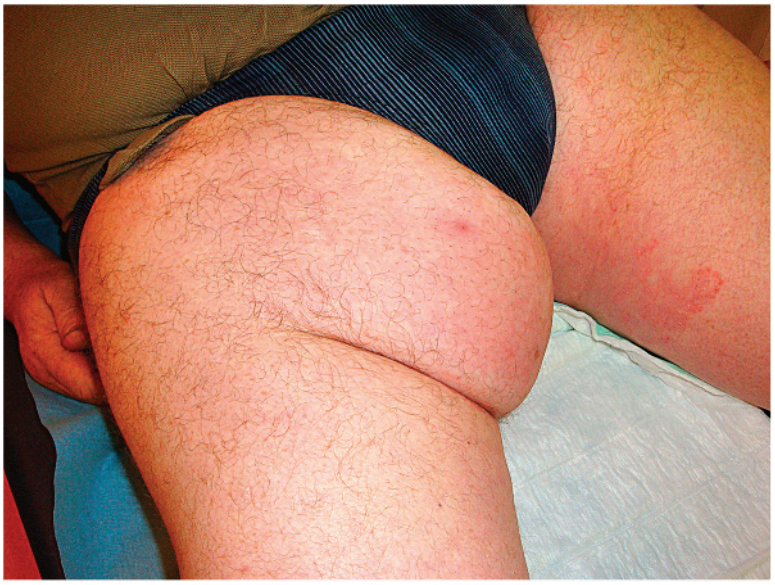

FIG. 1.2 Well-differentiated liposarcoma of the thigh.

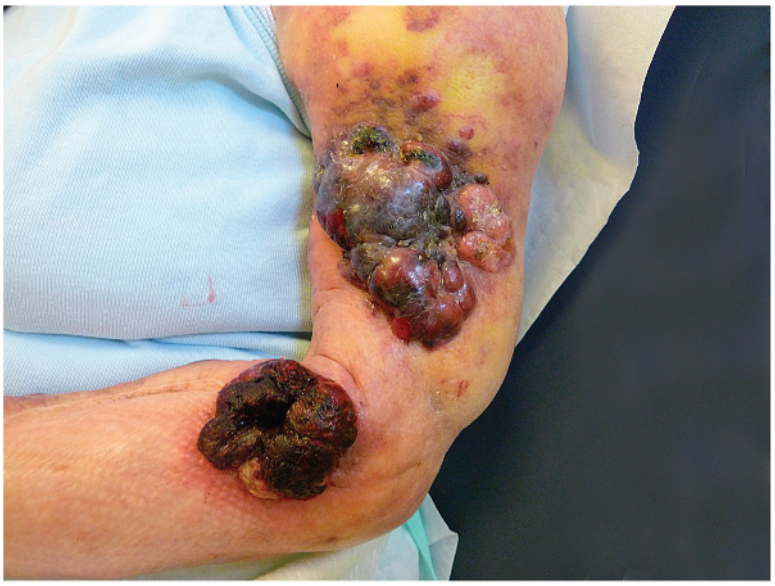

FIG. 1.3 Superficial dedifferentiated liposarcoma in an advanced stage.

trunk. Occurrence in subcutaneous tissue is extremely rare. Atypical lipoma/well-differentiated liposarcoma usually presents as a deep-seated, painless, and slow-growing enlarging mass of very large size, particularly when developing in the retroperitoneum. Retroperitoneal lesions often are asymptomatic until the tumor has exceeded 20 cm in diameter and may be found incidentally, hence, the poor outcome even for low-grade neoplasms. Initial symptoms are delayed and associated with large tumors and include vague and nonspecific abdominal pain, weight loss, nausea, a sometimes palpable abdominal mass, and compression of the kidney and ureter. Therapeutic management of retroperitoneal sarcomas is challenging because of their location and frequent intimate association with anatomical structures in the retroperitoneum. This proximity of large vessels, visceral organs, axial skeleton, and neural structures may impair significantly the ability to perform a margin-negative resection, which is the optimal potentially curative treatment approach in patients with localized disease. Even in the setting of a complete resection, local recurrence is common.

Dedifferentiated liposarcomas usually present as large painless masses, which may be found incidentally (particularly in the retroperitoneum). In the limbs, the history of a long-standing mass with a recent increase in size is suggestive of dedifferentiation. Radiologic imaging shows a coexistence of both fatty and nonfatty solid components, which in the retroperitoneum may be discontinuous.

Myxoid liposarcoma is the second most common subtype of liposarcoma, accounting for more than one third of liposarcomas and approximately 10% of all adult soft tissue sarcomas. Grossly, it is well circumscribed. It was considered a tumor of intermediate grade with a definite metastatic potential, particularly the round cell variant, but it pursues a relatively indolent behavior [33]. Its therapeutic approach has changed since the demonstration of its sensitivity to trabectidin. Myxoid liposarcoma occurs with a predilection in the deep soft tissues of the

extremities and in more than two thirds of cases originates within the musculature of the thigh. It rarely develops primarily in the retroperitoneum or in the subcutaneous tissue. It is prone to recur locally, and one third of patients develop distant metastases particularly with the round cell subtype. In comparison with other types of liposarcoma or other myxoid sarcomas of the extremities, myxoid liposarcoma tends to metastasize to unusual sites, like soft tissue (such as retroperitoneum, opposite extremity, axilla, etc.) or bone (with predilection to spine) locations, even before spreading to lungs. In a significant number of cases, myxoid liposarcoma patients present clinically with synchronous or metachronous multifocal disease. This unusual phenomenon most likely represents a pattern of hematogenous metastases to other sites by tumor cells seemingly incompetent to seed the lungs. The tendency for myxoid liposarcoma to metastasize to other soft tissues in preference to lung parenchyma has been well described [34]. A series of the Royal Marsden Hospital covering a 10-year period and including 50 patients with myxoid liposarcoma, with a median follow-up of 43 months, has shown that the actuarial 5-year soft tissue metastasis rate was 31%, and that the most common sites of myxoid liposarcoma were the retroperitoneum, abdominal wall, and abdominal cavity. In 12 patients with soft tissue metastases, there was a median interval of 23 months after the original diagnosis before the occurrence of the first metastases (range, 0–142 months). The median survival after the first metastasis was 35 months; 6 of the 12 patients died between 6 and 50 months. In this series, any round cell component of the myxoid liposarcoma was associated with a significantly greater risk of metastatic disease ($p = .02$), which has not been confirmed by other studies. The overall 5-year and 7-year survival rates were 85% and 68%, respectively. Patients with soft tissue metastases had an 11-fold greater risk of dying than those who did not. Therefore, the subset of patients who develop soft tissue metastases have a significantly worse prognosis [34].

Pleomorphic liposarcoma represents the rarest subtype of liposarcoma, accounting for approximately 5% of all liposarcomas and 20% of pleomorphic sarcomas. Pleomorphic liposarcoma tends to occur on the extremities (lower > upper limbs), whereas the trunk and the retroperitoneum are affected less frequently. Rare sites of involvement include the mediastinum, the paratesticular region, the scalp, the abdominal/pelvic cavities, and the orbit. Although most cases originate in deep soft tissues, examples in subcutis are rare. As for other deep-seated sarcomas, most patients complain of a firm, enlarging mass, with many cases presenting a notably short preoperative history. In general, pleomorphic liposarcoma is an aggressive mesenchymal neoplasm showing a 30–50% metastatic rate and an overall tumor associated mortality of 40–50%. Many patients die within a short period of time, and the lung represents the preferred site of metastases. In contrast, dedifferentiated liposarcomas and high-grade myxofibrosarcomas have a prolonged clinical course, whereas pleomorphic myogenic sarcomas of deep soft tissues show an even more aggressive clinical course emphasizing the need for subclassification of pleomorphic sarcomas.

Angiosarcomas occur in the following different clinical settings: tumors of the skin affecting mostly older patients (Figure 1.4), deep soft tissue tumors or organ-based neoplasms, and postradiation tumors. The mean age of patients with angiosarcoma of the scalp is approximately 70 years. The tumor manifested clinically as a bruise-like lesion in early phase and as indurated, erythematous plaque accompanied by nodules, ulcerations, and bleeding in advanced phase. Besides cutaneous

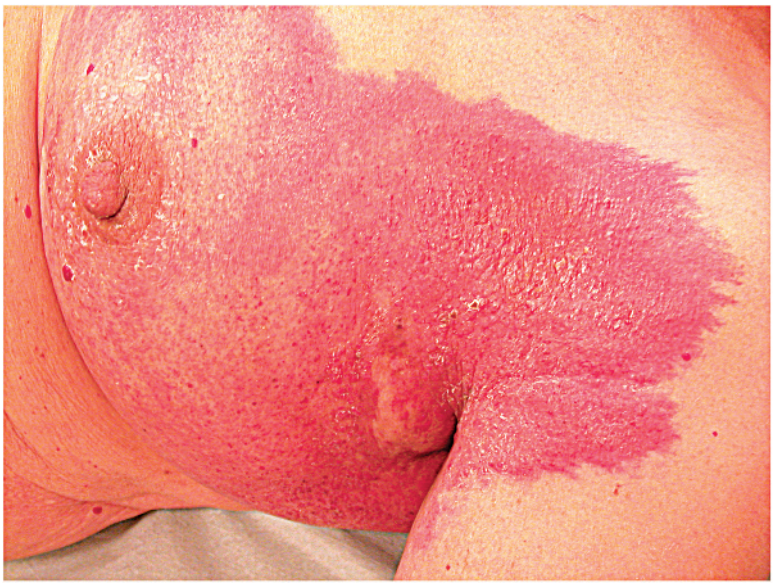

FIG. 1.4 Skin angiosarcoma in a patient with breast carcinoma history.

angiosarcomas, the angiosarcoma of the liver has been described in vinyl chloride workers worldwide [35]. Angiosarcomas are frequently sensitive to Paclitaxel treatments [36].

Hemangiopericytoma is a rare vascular tumor, and its histological distinction from synovial sarcoma and solitary fibrous tumor is a significant problem because they share similar histologic features. As will de discussed later, over the years, it has become a morphologic diagnosis of exclusion. Between July 1982 and February 1998, 62 patients with a diagnosis of primary, recurrent, or metastatic hemangiopericytoma were identified from a prospectively maintained database [37]. Using well-defined and recognized pathologic criteria, including immunohistochemistry and electron microscopy, tumors from 25 of 57 patients had a diagnosis of conventional hemangiopericytoma. At the time of initial presentation, 19 patients had primary tumors, 3 had locally recurrent diseases, and 3 had metastases. The most frequent anatomic sites of occurrence were the extremities, the pelvis, and the head and neck, accounting for 80% of the total cases. Two and 5-year overall survival rates ($n = 25$) were 93% and 86%, respectively. Patients undergoing complete resection ($n = 16$) showed a 100% median survival at 60 months. So far, complete tumor resection for patients with conventional hemangiopericytoma is recommended. However, considering their favorable biological behavior, surgical procedures that can generate altered anatomical functions or limb threatening are not recommended [37].

GIST is the most common sarcoma of the intestinal tract. It originates in the stomach, the small gut, and occasionally the large intestine. Rare cases also are reported in other locations, namely the esophagus, the abdominal cavity, and the retroperitoneum. Numerous GISTs are clinically symptomatic (69%), others are incidental findings at surgery (21%) or are found at autopsy (10%). Forty-four percent of symptomatic, clinically detected GISTs were categorized as high risk (29%) or overtly malignant (15%), with tumor-related deaths occurring in 63% of patients and 83% of patients, respectively (estimated median survival of 40 months

and 16 months, respectively). Tumor-related deaths occurred in only two of 170 of patients (1.2%) with very-low-risk, low-risk, or intermediate-risk tumors [3].

1.2.4 Paraneoplastic Syndromes

A large variety of sarcomas can reveal or be associated with paraneoplastic syndromes. Neurologic, endocrinologic, dermatologic, and urinary symptoms as well as clinical signs are common [38–40].

The neurologic system is the target of many immunologic paraneoplastic syndromes in sarcoma patients, such as opsoclonus-myoclonus syndromes [38], which are reported in neurofibrosarcoma patients as are antineural antibodies in an anti-Hu syndrome with neurologic deficits [39], and sensorimotor polyneuropathy. Central neurologic symptoms such as dysphasia may reveal a central nervous system vasculitis. Central nervous system vasculitis usually is diagnosed by MRI/magnetic resonance angiography (MRA) and cerebral angiography. Complete neurologic recovery may be achieved with Prednisone [38–40]. Endocrin manifestations also are very diverse [41–43]. Ectopic hormone productions may induce Cushingoid symptoms [41]. Arterial hypertension may be secondary to renin-producing leiomyosarcomas [42]. Hypoglycemia may be a consequence of a secretion of insulin-like growth factor, which also has been reported in leiomyosarcoma patients [43]. Clinical symptoms of inflammation also are possible. Dermatologic and rheumatologic syndromes also have been reported [44–50], including hand and foot ulceration, fixed cyanosis, and pallor complicating a central nervous system rhabdomyosarcoma and oncogenic osteomalacia. Acrokeratosis paraneoplastica (Bazexs syndrome) is a rare obligate paraneoplastic dermatosis characterized by erythematosquamous lesions localized symmetrically at the acral sites [50]. The condition almost exclusively affects Caucasian men older than 40 years. The surgical removal of a liposarcoma associated with acrokeratosis paraneoplastica shows a parallel regression or the development of the tumor in case of a recurrence of the liposarcoma [50]. Paraneoplastic pemphigus is a rare, life-threatening autoimmune bullous skin disease, which is an obligate paraneoplasm. The patient may present with recalcitrant stomatitis and a generalized lichenoid rash. In renal syndromes, for example, a membranous nephropathy [51–53], proteinuria, may disappear with the remission of the tumor. Nephrotic syndrome and acute renal failure have been associated with embryonal rhabdomyosarcoma. Effective treatment of the sarcoma was associated with sustained remission of the nephrotic proteinuria. A differential diagnosis for proteinuria is the obstruction of the renal veins, frequently caused by thrombosis or tumor processes. Although the obstructive mass initially may be misdiagnosed as thrombosis, positron emission tomography helps to reveal the tumor character of the lesion and a fine needle aspiration (FNA) allows for rapid diagnosis of a leiomyosarcoma originating from the caval or renal veins [54]. Stauffer syndrome [55], a very rare paraneoplastic syndrome, refers to reversible intrahepatic cholestasis in the setting of an abdominal malignancy and also was described in sarcoma patients. Prolonged fever or biological manifestations of inflammation also may be part of a paraneoplastic syndrome [56–58]. A white blood cell count of more than $50 \times 10(9)/l$, not related to bone marrow involvement, is referred to as leukemoid reaction. Pyrexia, leukocytosis, and other inflammatory findings may be associated with a sarcoma showing positive immunostaining for human granulocyte-colony simulating

factor (G-CSF). Northern and polymerase chain reaction (PCR) analyses also may detect CSF and its mRNA in the tumor. Therefore, it should be kept in mind, in case of adjuvant chemotherapy, that G-CSF (frequently prescribed to prevent doxorubicin-ifosfamide–induced profound neutropenia) shoud be avoided, if the patients had, at initial diagnosis, clinical symptoms or biological manifestations compatible with the presence of G-CSF receptors at the tumor surface.

1.3 CLINICAL DIFFERENTIAL DIAGNOSIS

In most cases, patients with soft tissue sarcoma will complain of a new and persistent lump, usually on an arm, leg, or trunk. This lump may or may not be painful. In patients with physical activity, the lump sometimes is mistaken for an injury related to athletic, professional, or recreational activities. We emphasize the following frequent situations: superficial sarcoma misinterpreted as hematoma or another benign condition and a deep retroperitoneal mass. First-line clinical subdifferentiation is important because the different subtypes vary in prognosis and therapeutic strategies [59] and allow for optimal patient management. Soft tissue sarcomas often present as a painless and slowly enlarging mass. Several sarcomas, like synovial sarcoma may be misdiagnosed clinically with other benign conditions, such as the Baker cyst or villonodular pigmented synovitis, considering their deceiving macroscopic and chronological features. Patients with sarcoma reporting trauma may be considered to have muscular posttraumatic hematomas [60–62]. Thus, posttraumatic intramuscular hematomas should be approached with a high degree of clinical suspicion and be evaluated radiologically (see Chapter 2). Briefly, the ultrasonographic investigation in an emergency is useful and may suggest the nature of the lesion [63]. Secondary MRI analysis also can be used as an important diagnostic tool, but both radiological investigations must be interpreted in the context of the clinical history. The MRI may reveal a small tumor mass with enhancement and characterize the hematoma in the lesion in a more precise fashion than does CT. Therefore, MRI imaging is a suitable method for differentiating these soft tissue sarcomas from chronic traumatic hematoma [62]. However, MRI is not sensitive or specific enough to rule out malignancy. As an initial approach, the search for malignant cells using percutaneous fine needle aspiration is indicated. If the cytological diagnosis of a sarcoma is suggested, then a histological biopsy will be considered [61]. Besides intramuscular hematomas, patients may present with hematoma at the site of a visceral sarcoma. For instance, intrathoracic sarcoma may be revealed by a chronic expanding thoracic hematoma [64]. Similarly, chronic subdural hematoma may lead to the diagnosis of subdural rhabdomyosarcoma, granulocytic sarcoma, or other subtypes of sarcoma [65–67].

Retroperitoneal sarcomas account for approximately one third of all retroperitoneal masses [68–72]. Although most extravisceral large masses in the retroperitoneum represent a retroperitoneal sarcoma, a differential diagnosis, including lymphoma, testicular neoplasm, germ cell tumor, desmoids, functioning and nonfunctioning adrenal masses, renal tumor, pancreatic tumor, and gastrointestinal stromal tumor, should be considered [68–72]. Among adrenal masses, exceptionally an adrenal sarcoma is identified as most often either a synovial sarcoma [73] or an angiosarcoma [74]. If visceral invasion is present, then a differential diagnosis should

be made that includes tumors of these organs and site-directed endoscopy with or without biopsy, if feasible, to evaluate for intraluminal evidence of involvement (e.g., stomach, duodenum, pancreas, colon). Symptoms suggestive of lymphoma include the classic B symptoms of unexplained fever, drenching night sweats, and weight loss in addition to the symptoms of unexplained pruritus and alcohol-induced pain at the sites of disease. For patients with testicular neoplasms, the physical examination should include a testicular examination for masses and consideration of testicular ultrasound. In addition, if a testicular neoplasm or germ cell tumor is considered then initial laboratory studies should include serum tumor markers, such as alpha fetoprotein (AFP), beta-human chorionic growth hormone (beta-HCG), and lactate dehydrogenase (LDH). The initial diagnostic evaluation of patients who are suspected of having retroperitoneal sarcoma should include a contrast-enhanced CT of the abdomen and pelvis to evaluate the size and extent of the lesion [68]. The use of oral and intravenous contrast is necessary to allow adequate visualization of the surrounding vascular structures, visceral organs, and skeletal structures for the assessment of respectability [68–72]. The CT appearance of liposarcomas typically includes fat-density components, but other retroperitoneal sarcoma histologic findings can be difficult to distinguish from other retroperitoneal tumors. MRI of the abdomen has been evaluated as a method of staging; however, MRI often does not add additional information to that obtained with contrast-enhanced CT of the abdomen. When enhanced-contrast CT is not available, MRI may provide an alternative modality to assess the local disease extent [68]. A biopsy for these lesions in the preoperative setting is controversial if there is a low index of suspicion for other tumors based on the initial evaluation; however, if neoadjuvant therapy is used, then histologic verification is usually necessary. In this event, a CT-guided cytology and biopsy is the preferred diagnostic approach. Surgical resection is considered the only potentially curative treatment modality, and complete surgical resection with negative margins remains the goal of therapy for most patients [69–71]. The likelihood of a negative margin surgical resection depends on several factors, including invasion of adjacent visceral organs, vascular structures, and skeletal structures.

1.4 THE IMPORTANCE OF MOLECULAR DIAGNOSIS AND ITS PERSPECTIVES

Molecular assays are described in Chapter 4. Briefly, the specific gene fusions provide a genetic approach to the differential diagnosis of soft tissue sarcomas. The genetic categories may correspond closely to the standard histopathologic categories. The polymerase chain reaction assays for chimeric transcripts are useful tools for the rapid and objective assessment of pediatric soft tissue sarcomas [75]. However, for many tumors, the histogenesis is controversial [76, 77].

1.5 TREATMENT STRATEGIES

The American Joint Commission on Cancer determines the stage of tumors by assessing the tumor's grade, size, and extension to nearby lymph nodes or to distant

organs [78]. The French Federation of Cancer Centers system is a different method that relies on microscopic grading to predict the apparition of metastastatic disease, even when other tests cannot detect that the sarcoma has spread. A high likelihood of metastastatic disease can influence the treatment that is recommended. The Musculoskeletal Tumor Society Staging System assigns tumor stage based on tumor grade, presence of metastases, and whether the tumor has extended beyond the anatomical region. Because muscle groups in the skeleton are divided into separate compartments by "sleeves" of connecting tissue, any growth or spread beyond the compartment of origin can be evidence that a tumor is spreading aggressively. For most soft tissue sarcomas, surgery is the basic treatment. The entire tumor is removed along with a wide excision. Improvements in curative surgery results are dependent on the delay for diagnosis on the conditions of biopsy or first excision [79]. Radiotherapy has a role inside a multimodal strategy [80]. After surgery, continued treatment usually depends on the type of sarcoma, the tumor stage and grade, tumor location, and the patient's age and general health. Tumor grade is the key to the tumor's current spread and future behavior. High-grade soft tissue sarcomas tend to spread early to distant sites. Metastatic disease is common, and conventional chemotherapy provides for only a narrow therapeutic window outside of a few responsive pathological subtypes.

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