REVIEW

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Soft tissue sarcoma: Recognizing a rare disease

ABSTRACT

The recognition of a malignant soft tissue mass can be challenging, given the rarity of soft tissue sarcoma and the extensive overlap between benign and malignant presentations. Awareness of the signs and symptoms of soft tissue sarcoma in primary care practice ensures prompt referral to a sarcoma center for appropriate assessment and treatment to optimize outcomes.

KEY POINTS

The rarity of soft tissue sarcoma, its heterogeneity, and overlap of symptoms with benign conditions are challenges to timely diagnosis.

A smaller tumor at diagnosis (< 5 cm) is associated with better prognosis.

Patients suspected of having a soft tissue sarcoma require prompt referral to a sarcoma center for assessment and treatment.

doi:10.3949/ccjm.89a.21078

The finding of a soft tissue mass on the trunk or limbs can be the source of anxiety and distress for patients, and a diagnostic challenge for clinicians. While in most cases the masses are benign,[1] early recognition of the signs and symptoms of soft tissue sarcoma (STS) and prompt referral to a center with expertise in STS are essential to ensure effective multidisciplinary team management and optimize outcome.

THE EPIDEMIOLOGY OF SOFT TISSUE SARCOMA

STS is rare. About 3,300 cases per year are reported in the United Kingdom,[2] and 13,500 new cases were reported in the United States in 2021, with 5,300 deaths, for an incidence rate of 15 to 35 per 1 million of the adult population.[3]

In the United States, the average overall 5-year survival rate for STS is approximately 65%.[3] The rate is 81% for patients who present with localized STS vs 15% for those who present with distant metastases.[3] Survival rates vary depending on tumor type, size, grade, response to treatment, and some patient demographic factors. Almost half of patients who present with intermediate-grade or high-grade tumors develop metastatic disease, although this rate is highly dependent on the presenting site and timing of diagnosis.[4]

STS accounts for only 1% of all adult cancer diagnoses,[5] and primary care physicians are likely to diagnose only 1 patient with STS in their entire career. But STS is also an important and often overlooked cause of death in patients ages 14 to 29,[5,6] and it represents 7% to 10% of all childhood cancers.[7] Therefore,

TABLE 1

Clinical features of soft tissue masses that require urgent investigation

Increasing size
Size greater than 5 cm (ie, golf-ball size)
Deeper-lying mass (deep to fascia)
Firmer than surrounding tissue
Patient has potential risk factors (previous radiotherapy, chronic lymphedema, inherited syndrome such as Gardner syndrome, Li-Fraumeni syndrome, and von Recklinghausen disease)
Local symptoms and signs of infiltration
With or without pain (large painless lumps should raise concern)

The greater the number of clinical features, the greater the risk of malignancy.

lumps and bumps presenting in all age groups should be viewed with a degree of caution.

CHALLENGES TO CLINICAL RECOGNITION OF SOFT TISSUE SARCOMA

The average 5-year survival for a patient with an STS is approximately 65%

STS is a heterogeneous group of tumors of mesenchymal cell origin that can occur anywhere in the body, affecting the extremities in 50% of cases, the trunk and retroperitoneum in 40%, and the head and neck in 10%.[3]

Awareness of STS is low among both the general public and healthcare providers. The wide range in presentation sites, lesion size, and patient ages and the overlap of symptoms with those of benign conditions make this diagnosis challenging. Lumps may often be dismissed or misdiagnosed as harmless cysts or fatty tissue. A UK survey found that patients with STS were significantly more likely to be treated for another condition or advised that their symptoms were not serious.[8] In 2006, Grimer et al[9] published a sarcoma database review that included a plea for greater recognition of potential malignant lumps and bumps, especially those larger than a golf ball (5 cm). This led to a campaign to raise public awareness of STS in the United Kingdom.[10] But despite attempts to increase recognition of STS, the typical size at presentation (10 cm) has changed very little.

FEATURES THAT GUIDE THE DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a soft tissue mass can include infections such as abscess, benign lesions such as ganglion, lipoma, and schwannoma, trauma (myositis ossificans), other cancers, and secondary cancers. Infections tend to present with a fluctuant mass along with systemic symptoms of fevers and night sweats. A thorough history and physical examination can usually narrow the differential diagnosis and guide further investigation.

A detailed examination of a lump includes its site, size, shape, contour, color, consistency, tenderness, tethering, transillumination, and fluctuance. Specific examination findings such as transillumination (ganglion), bruits or palpable thrills (hemangiomas, arteriovenous malformations), variability in size (ganglion, hemangiomas), a "doughy" softer consistency (lipoma), and a positive Tinel sign (schwannoma) may help to narrow the diagnosis further.[1]

STS tends to present as a large, painless, unexplained mass anywhere in the body that has been increasing in size. The belief that only painful masses are worrisome is wrong. The UK guidelines[5] suggest that a lump that is larger than 5 cm, exhibits growth, is deep in the body, and is painful should be considered malignant until proven otherwise (**Table 1**). Increasing size is the best individual indicator of a greater risk of malignancy.[5] A mass growing slowly over a period of weeks to months, painful or not, should raise more concern than a painful mass growing rapidly over a period of days. No change in the size of a tumor over a longer time period favors a benign diagnosis.

Adding to the diagnostic challenges is a lack of known risk factors for STS. In most cases, there is no identifiable underlying cause. The risk of developing sporadic STS is increased in patients with a history of previous radiotherapy and chronic lymphedema. Certain genetic mutations, particularly chromosomal translocations, and inherited syndromes such as Gardner syndrome, Li-Fraumeni syndrome, and von Recklinghausen disease can also predispose patients to STS.[11] Systemic signs such as weight loss, fatigue, fevers, chills, and night sweats are uncommon.[1]

Late diagnosis affects the prognosis

Studies have found an almost linear relationship between the increasing lesion size and poorer prognosis that is independent of other factors, even for patients without metastatic disease at diagnosis.[9] This is particularly true of tumors larger than 5 cm, emphasizing the point that a smaller tumor at diagnosis and treatment is associated with better prognosis.[9] A smaller lump is easier to remove and reduces the surgical and long-term functional impact on the local anatomical area. Other factors associated with worse clinical outcomes are high-grade histology, positive margins after resection, and patient age over 60.

Unfortunately, in the United Kingdom, the average wait for a patient from noticing symptoms to referral and subsequent investigations is 92 weeks. By the time of diagnosis, the average tumor size is 10 cm or larger.[9,12] According to guidelines, a patient with a concerning lump or mass that is increasing in size, larger than 5 cm, in the deep fascia, and painful should be referred immediately to a sarcoma center for further evaluation, even if the risk of malignancy is only 3% to 4%.[5,13] Early referral is important to improve the outcomes.

WHICH DIAGNOSTIC TESTS ARE PREFERABLE?

Ultrasonography

A patient suspected of having STS should initially undergo ultrasonography. Blood tests provide no benefit in the diagnosis of STS and thus are not recommended. Ultrasonography is proven to be cost effective, with a high negative predictive value for soft tissue masses.[14,15] The diagnostic specificity is further increased if the procedure is performed by an experienced musculoskeletal radiologist.

The National Institute of Clinical Excellence (NICE) recommends that all adults be referred for ultrasonography within 2 weeks of presentation and within 48 hours in pediatric patients. Referral can made to a sarcoma center. If ultrasonography raises suspicion of STS or is inconclusive, the patient must be referred to a sarcoma center.[5] Features that raise concern are increased size, irregular margins, heterogeneity (ie, tissue existing where it should not), and architectural distortion. Outgrowth of blood supply with concomitant central necrosis seen on color Doppler ultrasonography is usually indicative of a higher-grade sarcoma.[16] If requesting ultrasonography in the primary care setting could introduce delay, then urgent referral to a sarcoma center is recommended.

The most common soft tissue lesions diagnosed from an initial workup are lipomas, ie, benign tumors of fat cells. Both ultrasonography and magnetic resonance imaging (MRI) have a high sensitivity and specificity for this diagnosis. Studies have shown that ultrasonography has an overall sensitivity of 86% and a specificity of 96% in the diagnosis of lipomas.[17]

The role of magnetic resonance imaging

If the diagnosis remains uncertain or if there are concerning features, then the most sensitive and specific imaging modality available is MRI. MRI with contrast enhancement is preferred over noncontrast MRI to assess characteristics of the mass. Obtaining contrast MRI results first helps save time and reduces the need for repeated investigations. MRI is considered the technical standard for localizing and staging STS as it enables accurate analysis of the soft tissue structure as well as its relationship to surrounding local structures. It is often used for biopsy and surgical planning.[15,18] MRI has a very high negative predictive value (100%) for distinguishing a benign lipoma from a malignant lipoma.[19]

Delayed diagnosis is a common reason for malpractice claims related to sarcoma care

The role of biopsy

The standard diagnostic approach must also include biopsy, in most cases multiple percutaneous core needle specimens obtained under ultrasonographic guidance.[5] In some cases, incisional or excisional (open) biopsy may be required. Biopsy should be performed by a team composed of a tumor-trained orthopedic surgeon, radiologist, and pathologist to ensure that optimal samples are taken and analyzed without compromising the final surgical treatment and unnecessary contamination of healthy tissue. Poorly performed biopsies can lead to a higher risk of adverse outcomes and expenses.[20]

A high degree of suspicion for STS based on the biopsy results should trigger prompt referral to a sarcoma center for triple assessment of clinical history, imaging, and biopsy, all of

which should be done on the same day.[5] And if STS is diagnosed, these centers have multidisciplinary teams trained to maximize long-term survival, minimize local recurrence, optimize function, and minimize morbidity, and they also have resources to perform additional staging studies to identify distant spread of proven STS. This additional information helps tailor treatment to the individual patient.

AVOIDING A 'WHOOPS PROCEDURE'

The term "whoops procedure" describes when a mass assumed to be benign is resected and the final pathologic diagnosis comes back, unexpectedly, as sarcoma or other pathology. At one sarcoma center, approximately three-quarters of referrals originated from a whoops procedure undertaken in a primary or secondary care unit.[21] Misdiagnosis occurs most often in soft tissue tumors that are smaller than 5 cm, painless, and superficial to the fascia.[22] A retrospective review of almost 400 cases found that a lack of appropriate preoperative workup, including imaging and biopsy, was responsible for whoops procedures.[23] In short, they are essentially a result of low awareness among practitioners for the presence of a potential STS.

Whoops procedures have been shown to cause the following:

- Lower rates of local control and limb salvage
- A shorter mean time to recurrence and subsequent metastasis
- An increase in wound complications and amputation rate
- A higher rate of postoperative wound complications and greater need for flap coverage
- Overall poorer functional outcomes.[21,24]

To avoid a whoops procedure, a patient with a suspected soft tissue lump of unknown pathology should be referred to a sarcoma center for appropriate imaging and assessment. Appropriate biopsy procedures also dramatically reduce the degree of mismanagement and overall harm to patients.

LITIGATION AND COST

Medical malpractice claims related to STS care have been increasing in both the United Kingdom and the United States, and common reasons are poor awareness, lack of knowledge, false reassurance, and late referrals.[25,26] In one review, litigation rates dramatically fell if a patient had been referred to a sarcoma center.[26]

In the United States, the mean indemnity payment favoring the patient was approximately $2.30 million (£1.7 million) in 2020, with delay in diagnosis being the main reason (86%).[25] These cases were mostly filed against the primary care physicians.[23] Thus, educating practitioners and raising awareness of STS in order to prompt early referral are keys to providing better care and reducing malpractice claims.

TAKE-HOME MESSAGE

Effective management of patients with suspected STS requires practitioners to be aware of the signs and symptoms and to know the appropriate testing procedures. Referring patients with known or suspected STS to a sarcoma center, which has knowledgeable multidisciplinary teams and is equipped for accurate diagnosis and subsequent management, will ensure the most optimal outcomes. It is important to not delay a referral. Early referrals can also reduce the number and devastating impact of the so-called whoops procedures. ■

Features that raise concern for a malignant soft tissue mass include increasing size, irregular margins, and architectural distortion

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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