

the SARCOMA JOURNAL

*Official Journal
of The Sarcoma
Foundation
of America™*

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Diagnosis and treatment

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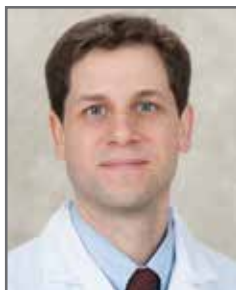
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Premier Issue



EDITORIAL VIEWS AND NEWS

BY WILLIAM D. TAP, MD | Editor-In-Chief

> I WELCOME YOUR PARTICIPATION IN THE SUCCESS OF THE SARCOMA JOURNAL BY SUBMITTING MANUSCRIPTS, INTERESTING CASE STUDIES, ORIGINAL RESEARCH, AND TOPIC PERSPECTIVES—AS WELL AS REVIEW ARTICLES—AND SHARE YOUR THOUGHTS ON HOW WE CAN BEST SERVE OUR COMMUNITY AND PATIENTS.

—WILLIAM D. TAP, MD, CHIEF, MEDICAL ONCOLOGY SERVICE AT MEMORIAL SLOAN KETTERING CANCER CENTER

Introducing The Sarcoma Journal—The Official Journal of the Sarcoma Foundation of America™: An Exciting Initiative in Peer-Reviewed Professional Education and Patient Advocacy

The *Sarcoma Journal — Official Journal of the Sarcoma Foundation of America™* represents a new and exciting initiative in professional education. We invite you to share in the excitement surrounding the launch of a medical journal designed to be your most authoritative and comprehensive source of scientific information on the diagnosis and treatment of sarcomas and sarcoma sub-types.

On behalf of myself, our editorial board, and editorial staff, I welcome you to this journal as we explore new treatment paradigms for this disease, translational research that bridges the bench and the clinic, and a broad range of science to encompass the many facets of sarcoma. In my opinion, the startup of this publication could not come at a better time.

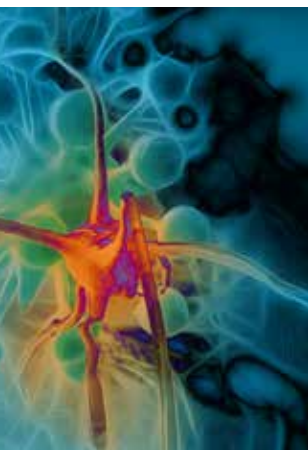
As cancer specialists and allied health care professionals who attend regular meetings of your peers, including ASCO and CTOS, we have seen a dramatic shift in management within the last few years. In many ways we are at a threshold of a new era in sarcoma management, and the spectrum of treatment is expanding across subspecialties, promising more effective strategies for our patients that are based on an improved understanding of disease biology. We need a resource to maintain and clarify our focus on this disease as research opens new avenues for us to consider in the management of patients with sarcoma.

When I was approached to serve as Editor-in-Chief of *The Sarcoma Journal* by the Sarcoma Foundation of America, I began to recruit an esteemed group of colleagues whose knowledge, worldwide reputation as thought leaders, and dedicated work as researchers would reflect our commitment toward finding a cure for sarcoma. Many of the colleagues who will join me on the Editorial Advisory Board have long-stand-

ing affiliations with the Sarcoma Foundation of America and its comprehensive program of sarcoma research, patient support and education and advocacy. As you explore the first issue of the journal, you will discover how our editorial content is an extension of this three-tiered approach. The SFA program is characterized by a multi-dimensional and uniquely coordinated outreach program of videos and webinars, websites (a new journal website is launching as well) a sarcoma-specific clinical trials database, newsletters and related materials— all aimed ultimately at finding a cure for this disease. This professional journal complements and extends the SFA's mission.

Although *The Sarcoma Journal* has a position within the SFA umbrella, my focus is foremost on ensuring that *The Sarcoma Journal* contains the most accurate, relevant and up to date information available. I urge you to explore our highly informative and relevant sarcoma-specific content—including original reports, review articles, a Journal Club, expert opinion, meeting reports, and patient advocacy that encapsulates the latest findings from the bench with implications for the bedside.

Whether it is discussing the latest findings in advanced sarcoma sub-types or implications of genetics as a prognostic factor, you will find the information in this journal, reliably analyzed by our team of experts who are leading sarcoma clinicians and investigators. All of the content we provide is presented in a thought-provoking, lively and peer-reviewed format; we welcome your comments and suggestions to keep us on the forefront of patient care as we cover a rapidly evolving landscape of new information in the treatment of sarcomas and frame it within a context directly applicable to enhancing the quality of patient care.



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DESCRIPTION

The Sarcoma Journal—Official Journal of the Sarcoma Foundation of America™ is the premier practical, peer-reviewed quarterly journal dedicated to meeting the needs of practicing oncologists. The journal is specifically focused on sarcomas and sub-types, with a clear and concise style to guide oncologists through detection, diagnosis, treatment, and management of the disease. The Sarcoma Journal — Official Journal of the Sarcoma Foundation of America™ provides useful information that can be immediately applied to the practice of oncology.

Manuscripts should be submitted to Frank Iorio at fiorio@frontlinemedcom.com.

INTRODUCTION

The Sarcoma Journal—Official Journal of the Sarcoma Foundation of America™ publishes peer-reviewed articles and commentaries on all aspects of clinical issues in sarcomas.

We encourage you to share your expertise with your oncology colleagues by submitting articles in the following categories:

Case Reports: Interesting, unique or informative cases that present and unfold in the examining room.

Reviews: Thorough reviews of topics that have broad interest to the practicing oncologist. Emphasis should be on the practical application of this information in the clinical arena.

Original Research: Clinical studies with sufficient power to be implemented in clinical practice and to be of interest to practicing oncologists. No animal or basic science studies will be considered, and all research studies must have been conducted with Institutional Review Board approval.

Diagnostic Findings: An interesting case or study, or an unusual physical finding with a brief synopsis.

PLEASE NOTE THE FOLLOWING:

- Papers submitted to The Sarcoma Journal—Official Journal of the Sarcoma Foundation of America™ should follow the style guidelines of the AMA Manual of Style (10th edition).
- Papers that exceed the stipulated word counts will be returned to the author(s) for editing before the paper is sent out for review.
- Papers in which the references do not follow style will also be returned to the author for revision.

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Soft Tissue Sarcoma: Diagnosis and Treatment

INTRODUCTION

Soft tissue sarcomas (STSs) are rare adult tumors, with 3.4 new cases per 100,000 persons or 12,310 expected new cases in 2016.¹ Sarcomas are a heterogeneous collection of tumors that affect fat, muscle, nerve, nerve sheath, vascular, and connective tissues. There are more than 50 histological subtypes that comprise this diverse category of tumors. Treatment varies by stage, with limb-sparing surgery representing the mainstay of curative-intent treatment. Radiation and chemotherapy may also be considered depending on the size, grade, and location of the tumor. Survival rates have been stagnant until recently, with a disease-specific survival hovering around 65%.¹ Given the complexity of these cases, all patients ideally should be evaluated and treated by a multidisciplinary team at an institution with extensive experience treating STS.²

EPIDEMIOLOGY AND CLASSIFICATION

The most common STS subtypes are gastrointestinal stromal tumor (GIST), undifferentiate pleomorphic sarcoma (previously referred to as malignant fibrous histiocytoma), liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, rhabdomyosarcoma, and unclassified sarcoma.³ Liposarcoma is one of the most common subtypes, comprising 20% of all STSs; it is subdivided into well-differentiated/dedifferentiated liposarcomas, myxoid/round cell liposarcomas, and pleomorphic liposarcomas. Well-differentiated liposarcomas tend to occur in the retroperitoneum and limbs, while both myxoid and round cell as well as pleomorphic liposarcomas more commonly originate on the limbs. Histology

varies based on subtype and ranges from mature-appearing adipocytes and fibroblasts to undifferentiated cells with minimal lipogenic differentiation.⁴

Leiomyosarcomas are smooth muscle tumors and are usually located in the retroperitoneum, but have also been associated with peripheral soft tissue and vasculature. Typical histology ranges from well-defined areas of spindle-shaped cells to poorly differentiated anaplastic spindle cells.^{5,6} Synovial sarcomas are a distinct type of STS that can show epithelial differentiation and account for 5% of adult STSs. The extremities are the most common presenting location (90%).⁷

Rhabdomyosarcomas are skeletal muscle tumors and are further subdivided into embryonal, alveolar, and pleomorphic subtypes. Embryonal histology ranges from primitive mesenchymal-appearing cells to highly differentiated muscle cells. Alveolar rhabdomyosarcoma has the worst prognosis of the subtypes and consists of round cells with high nuclear-to-chromatin ratios that form “glandular-like” or “alveolar” spaces.⁸ Pleomorphic rhabdomyosarcomas are composed of rhabdomyoblasts that can affect many different locations, but most commonly present on the lower extremities.⁹

Malignant peripheral nerve sheath tumor (MPNST) comprises 5% to 10% of all STSs. These tumors are associated with neurofibromatosis type 1 (NF-1), with 25% to 50% of tumors occurring in NF-1 patients. Additionally, most patients have a truncating lesion in the *NF1* gene on chromosome 17.¹⁰ Anghileri et al in their single institution analysis of 205 patients with MPNSTs found the 2 most common presenting sites were the trunk and extremities. Histologically, these tumors have dense fascicles of spindle cells.¹⁰

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DISCLOSURES

The authors report no disclosures or conflicts of interest.

GISTs are the most common STS of the gastrointestinal (GI) tract. Previously, GISTs were classified as smooth muscle tumors and were not accounted for in the literature as a separate entity distinct from leiomyomas, leiomyoblastomas, and leiomyosarcomas.¹¹ GISTs are found throughout the GI tract: the most common sites are the stomach (60%) and small intestine (30%). Less common sites include duodenum (4%–5%), esophagus (1%), rectum (1%–2%), and appendix (< 0.2%).¹² GISTs can be spindle cell, epithelioid, or mesenchymal tumors. Immunohistochemically, GISTs are KIT (CD117) positive. Other cell markers that are also commonly positive include CD34 (60%–70%) and smooth muscle actin (SMA) (25%).¹¹ The majority of GISTs (80%) have an activating *c-KIT* gene mutation. The most common mutation site is exon 11, with less common *c-KIT* gene mutations also occurring at exon 9 or 13. Not all GISTs have *KIT* mutations. The second most common mutation is the *PDGFRA* mutation (5%–10% of GISTs).² A minority of GISTs are negative for both *KIT* and *PDGFRA* mutations. These tumors were previously called wild-type, but as the majority have either a succinate dehydrogenase (SDH) loss of function or loss of SDHB protein expression, they are now referred to as SDH-deficient GISTs.² GISTs vary in aggressiveness from incidental to aggressive. Typically, small intestine and rectal GISTs are more aggressive than gastric GISTs. Both size and mitotic rate help to predict the metastatic potential of the tumor. Tumors less than 2 cm in size and having a mitotic rate of less than 5 per 50 high-power fields (hpf) have the lowest risk of metastases, while tumors greater than 5 cm and with more than 5 mitoses per 50 hpf have the highest rates of metastases.¹²

Angiosarcomas are rare tumors comprising 4% of all STSs. Although they can occur in any site, the majority are cutaneous and occur most frequently in the head and neck regions. These tumors are either of vascular or lymphatic origin and are comprised of abnormal, pleomorphic, malignant endothelial cells. The most useful immunohistochemical markers include von Willebrand factor,

CD31, and *Ulex europaeus* agglutinin 1. The majority of these tumors occur sporadically; however, radiation exposure, chronic lymphedema, and certain toxins including vinyl chloride and thorium dioxide are known risk factors.¹³

Undifferentiated sarcomas have no specific features and typically consist of primitive mesenchymal cells.

CLINICAL EVALUATION

► CASE PRESENTATION

Initial Presentation and History

A 55-year-old man presents to his primary care physician with a painless mass in his anterior thigh. The mass has been present for the past 3 months and he believes that it is enlarging. The patient has a history of well-controlled hypertension and hyperlipidemia. His medications include atorvastatin and hydrochlorothiazide. He has no known drug allergies. Family history is notable for diabetes and hypertension. He drinks 4 to 5 alcoholic drinks a week and he is a former smoker. He quit smoking in his 30s and only smoked intermittently prior to quitting. He denies any illicit drug use. He works as a high school principal. Currently, he feels well. His review of systems is otherwise noncontributory.

Physical Examination

On physical exam, he is afebrile with a blood pressure of 132/75 mm Hg, respiratory rate of 10 breaths/min, and oxygen saturation of 99% on room air. He is a well appearing, overweight male. His head and neck exam is unremarkable. Lung exam reveals clear breath sounds, and cardiac exam reveals a regular rate and rhythm. His abdomen is obese, soft, and without hepatosplenomegaly. There is a large, fixed mass on the anterior lateral aspect of his right thigh. He has no appreciable lymphadenopathy. His neurological exam is unremarkable.

• What are risk factors for sarcoma?

There are few known risk factors for sarcoma. Established risk factors include prior radiation therapy, chronic lymphedema, viruses, and genetic cancer syndromes including Li-Fraumeni syn-

TABLE 1. Translocations and Cytogenic Events Associated with Forms of Soft Tissue Sarcoma

Sarcoma Type	Translocations/Cytogenetic Events	Genes Involved
Gastrointestinal stromal tumor	KIT, PDGFRA mutation; loss of SDH expression	KIT, PDGFRA, SDH
Synovial sarcoma	t(X;18)(p11.2;q11.2)	SSX1-, SSX2-, or SSX4-SS18
Alveolar soft-part sarcoma	t(X;17)(p11;q25)	ASPSR1-TFE3
Myxoid liposarcoma	t(12;16)(q13;p11)	TLS-CHOP
Clear-cell sarcoma	t(12;22)(q13;q12)	EWSR1-ATF1
Low-grade fibromyxoid sarcoma (Evans' tumor)	t(7;16)(q34;p11)	FUS-BBF2H7
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	COL1A1-PDGFB
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	EWSR1-WT1
Ewing sarcoma/round cell sarcomas or Ewing-like (previously called PNET)	t(11;22)(q24;q12)	EWSR1-FLI1, others
	t(21;22)(q22;q12)	EWSR1-ERG
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) or t(1;13)(p36;q14)	PAX3- or PAX7-FOXO1
Embryonal rhabdomyosarcoma	Trisomy 2q, 8 and 20	Loss of heterozygosity at 11p15
Inflammatory myofibroblastic tumor	ALK translocations (~50%)	Many partner genes

drome, hereditary retinoblastoma, and NF-1. Other environmental exposures include phenoxyacetic acids and chlorophenols.¹⁴ The majority of cases are sporadic, with only a minority of patients having one of these known risk factors.¹⁵ Up to one third of sarcomas have a specific translocation and are driven by fusion oncogenes (TABLE 1).

• What is the typical presentation for sarcomas?

A painless mass is the most typical presenting symptom. Size at presentation varies based on location, with extremity and head and neck locations typically presenting at smaller sizes than retroperitoneal tumors.¹⁴ Patients may experience pain and numbness as the mass enlarges and impinges on surrounding structures including nerves and vasculature. The vast majority of patients are without systemic symptoms.

• How is sarcoma staged?

The American Joint Committee on Cancer (AJCC) staging system is the most widely used staging system in the United States. The latest AJCC manual was updated in 2010 to include a 3-tiered grading system where the tumor is classified according

to tumor size, lymph node involvement, metastases, and grade at time of diagnosis (TABLE 2 and TABLE 3). Additionally, tumor depth in relation to deep fascia is also taken into account, with superficial tumors being assigned a designation of “a” and deep tumors a designation of “b.”

Previously, 2 of the most widely used grading systems were the National Cancer Institute (NCI) and French Federation of Cancer Centers Sarcoma Group (FNCLCC) systems, both 3-tier grading systems. The main components that determine the NCI grade are the tumor's histologic type and location and the amount of tumor necrosis. The FNCLCC system evaluation focuses on tumor differentiation, mitotic rate, and amount of tumor necrosis. A study that compared the NCI and FNCLCC grading systems found that FNCLCC was a better predictor of mortality and distant metastasis.¹⁶ Previously, the AJCC was a 4-tier grading system, but the 2010 version was updated to the 3-tier FNCLCC grading system. Additionally, the AJCC system has reclassified single lymph node disease as stage III as it confers better survival than metastatic disease.¹⁷ It is important that pathology be evaluated by a sarcoma specialist as disagreements with regard to histologic subtype and grade are common.^{18,19}

TABLE 2. Staging Soft Tissue Sarcoma: Definitions

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 5 cm in greatest dimension
T1a	Superficial tumor
T1b	Deep tumor
T2	Tumor > 5 cm in greatest dimension
T2a	Superficial tumor
T2b	Deep tumor
Note: Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.	
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N1	No regional lymph node metastasis
N2	Regional lymph node metastasis
Note: Presence of positive nodes (N1) in M0 tumors is considered stage III	
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Histologic grade (G)	
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3

Adapted with permission from AJCC. Soft tissue sarcoma. In: Edge SB, Byrd DR, Compton CC, et al, eds. AJCC cancer staging manual. 7th ed. New York (NY): Springer; 2010:291–8.

- **What are the most important prognostic factors?**
Prognostic factors include grade, size, and presence of metastases at presentation. Best survival is associated with low-grade, small tumors with no metastases at time of diagnosis.¹⁴
- **What imaging should be considered?**
Imaging should be undertaken to help differentiate between benign and malignant lesions. Ideally, it should be undertaken before a biopsy is planned as the imaging can be used to plan biopsy as well as provide invaluable prognostic information. There are several imaging modalities

that should be considered during the preliminary work-up and staging of STSs. Conventional imaging includes magnetic resonance imaging (MRI) of the original tumor site; computed tomography (CT) to evaluate for pulmonary metastases and, depending on location, liver metastases; and in the case of small, low-grade tumors, chest radiography. MRI is considered the test of choice for soft tissue masses and can help delineate benign masses such as hematomas, lipomas, and hemangiomas from sarcomas.²⁰ It is difficult to compare the accuracy of positron emission tomography (PET)/CT to CT and MRI because most studies have evaluated PET/CT in parallel with CT and MRI.²¹ Tateishi et al compared the accuracy of conventional imaging, PET/CT, and PET/CT combined with conventional imaging at determining the TNM staging for 117 patients. They found that conventional imaging correctly classified 77% of patients, PET alone correctly classified 70%, PET/CT correctly classified 83%, and PET/CT combined with conventional imaging correctly staged 87%.²²

- **Which subtypes are most likely to metastasize?**
Although the vast majority of sarcomas spread hematogenously, 3 have a propensity to spread lymphogenously: epithelioid sarcoma, rhabdomyosarcoma, and clear-cell sarcoma. Additionally, certain subtypes are more likely to metastasize: leiomyosarcomas, synovial sarcomas, neurogenic sarcomas, rhabdomyosarcomas, and epithelioid sarcomas.²³ Sarcomas metastasize to the lungs more frequently than to the liver. The metastatic pattern is defined primarily by sarcoma subtype and site of primary tumor. Sarcomas rarely metastasize to the brain (~1%).

MANAGEMENT

➤ **CASE CONTINUED**
The patient undergoes an ultrasound to better visualize the mass. Given the heterogeneous character of the mass, he is referred for an MRI to evaluate the mass and a CT scan of the chest, abdomen, and pelvis to evaluate for distant metastases. MRI reveals a 5.1 cm × 4.6 cm heteroge-

neous mass invading the superficial fascia of the rectus femoris muscle. No suspicious lymph nodes or other masses are identified on imaging. The patient next undergoes an image-guided core needle biopsy. Pathology from that procedure is consistent with a stage III, T2bNxMx, grade 3, dedifferentiated liposarcoma.

• **What is the best management approach for this patient?**

SURGERY

Surgery is the mainstay of treatment for STS. Patients with the best prognosis are those who undergo complete resection with negative surgical margins.^{24,25} Goal tumor-free margin is 1 to 3 cm.²⁶ Complete resection confers the best long-term survival. Both local and metastatic recurrence is higher in patients with incomplete resection and positive margins.^{24,25} In a study that analyzed 2084 localized primary STSs, patients with negative margins had a local recurrence rate of 15% versus a rate of 28% in patients with positive margins. This translated into higher 5-year local recurrence-free survival for patients with negative surgical margins (82%) compared to patients with positive margins (65%).²⁷ Another study similarly found that patients with negative margins at referral to their institution who underwent postoperative radiation had high local control rates of 93% (95% confidence interval [CI] 87% to 97%) at 5, 10, and 15 years.²⁶ Although radiation improves local control, neither preoperative or postoperative radiation has been shown to improve progression-free or overall survival.²⁸ Other factors that are associated with risk of recurrence are tumor location, history of previous recurrence, age of patient, histopathology, tumor grade, and tumor size. Approximately 40% to 50% of patients with high-grade tumors (defined as size > 5 cm, deep location, and high grade) will develop distant metastases.²⁹

Zagars et al found that positive or uncertain resection margin had a relative risk of local recurrence of 2.0 (95% CI 1.3 to 3.1; $P = 0.002$), and presentation with locally recurrent disease (vs new tumor) had a relative risk of local recurrence of 2.0 (95% CI 1.2 to 3.4; $P = 0.013$).²⁶ Pa-

TABLE 3. Soft Tissue Sarcoma Stages

Anatomic Stage/Prognostic Group				
Stage IA	T1a	NO	MO	G1, GX
	T1b			
Stage IB	T2a			
	T2b			
Stage IIA	T1a			G2, G3
	T1b			
Stage IIB	T2a			G2
	T2b			
Stage III	T2a, T2b			G3
	Any T	N1		Any G
Stage IV	Any T	Any N	M1	Any G

Adapted with permission from AJCC. Soft tissue sarcoma. In: Edge SB, Byrd DR, Compton CC, et al, eds. AJCC cancer staging manual. 7th ed.

tients with STS of head and neck and deep trunk have higher recurrence rates than those with superficial trunk and extremity STS. A single-institution retrospective review demonstrated that patients with completely resectable retroperitoneal sarcomas have longer median survival (103 months) compared to patients with incompletely resected abdominal sarcomas (18 months).²⁵

Rosenberg and colleagues compared amputation to limb-sparing surgery and radiation.²⁴ Their prospective analysis of 65 patients found no difference in disease-free and overall survival between the 2 treatment groups. The limb-sparing treatment group had higher rates of local recurrence, which was highly correlated with positive surgical margins on pathology.²⁴ Evidence from this and similar studies has resulted in radical amputations being replaced by conservative limb-sparing procedures and radiation therapy. In those found to have positive margins, re-resection is an option for some. Patients who undergo re-resection have higher local control rates than patients with positive margins who do not undergo re-resection. The 5-year control rate for patients who undergo re-resection is 85% (95% CI 80% to 89%) compared to 78% (95% CI 71% to 83%) for those who do not undergo re-resection. Similarly, patients who

➤ **A NEWER STRATEGY, INTENSITY-MODULATED RADIATION THERAPY (IMRT), UTILIZES 3-DIMENSIONAL MODELING TO REDUCE RADIATION DOSAGES.**

undergo re-resection have lower rates of metastases at 5, 10, and 15 years as well as higher 5-, 10-, and 15-year disease-free survival rates.²⁶

➤ **CASE CONTINUED**

The patient is referred for limb-sparing surgery after presentation at a multidisciplinary tumor board. Prior to undergoing resection of the tumor, he is also referred to radiation-oncology to discuss the risks and benefits of combination radiotherapy and surgery as opposed to surgical resection alone.

• **What is the evidence for radiation therapy?**

RADIATION THERAPY

Radiation therapy is used in the preoperative, intraoperative, and postoperative settings to reduce the risk of local recurrence. There are several options for radiation, including external beam radiation therapy (EBRT), intraoperative radiation, and brachytherapy. A newer strategy, intensity-modulated radiation therapy (IMRT), utilizes 3-dimensional modeling to reduce radiation dosages. Overall there are no differences in overall survival or local recurrence rates between preoperative and postoperative radiation in STS.²⁸

The rationale behind preoperative radiation is that it reduces seeding of tumor cells, especially at the time of surgery.³⁰ Additionally, for EBRT, preoperative radiation has smaller field sizes and lower radiation doses. It can also help to reduce the size of the tumor prior to resection. Intraoperative radiation is often paired with preoperative radiation as a boost dose given only to the area of residual tumor.

Suit et al reviewed patients treated at a single institution with limb-sparing surgery and different radiation strategies. Local control rates between preoperative and postoperative radiation groups were not statistically significant. Local recurrence was linked to grade and size of the tumor in both groups. The authors did note, however, that the preoperative radiation group tended to have larger tumor sizes at baseline compared to the patients who received postoperative radiation.³⁰ A study that compared 190 patients

who received preoperative and postoperative EBRT or brachytherapy (primary end point was wound complications, and local control was a secondary end point) showed a trend towards greater local control with preoperative radiation; however, the preoperative radiation group had significantly more wound complications compared to the postoperative radiation group.³¹

Yang et al found that postoperative EBRT decreases rates of local recurrence compared to surgery alone in high-grade extremity sarcomas.³² However, there were no differences in rates of distant metastases and overall survival between the 2 treatment groups. Similarly, in patients with low-grade sarcoma, there were fewer local recurrences in those who received EBRT and surgery as compared to surgery alone.³² Another study that evaluated 164 patients who received either adjuvant brachytherapy or no further therapy after complete resection found that brachytherapy reduced local recurrence in high-grade sarcomas. No difference in local recurrence rates was found in patients with low-grade sarcomas, nor was a significant difference found in the rates of distant metastases and overall survival between the 2 treatment groups.³³ With regards to IMRT, a single institution cohort experience with 41 patients who received IMRT following limb-sparing surgery had similar local control rates when compared to historical controls.³⁴

➤ **CASE CONTINUED**

After discussion of the risks and benefits of radiation therapy, the patient opts for preoperative radiation prior to resection of his liposarcoma. He receives 50 Gy of EBRT prior to undergoing resection. Resection results in R1 margin consistent with microscopic disease. He receives 16 Gy of EBRT as a boost after recovery from his resection.²

• **What is the evidence for neoadjuvant and adjuvant chemotherapy for stage I tumors?**

CHEMOTHERAPY

Localized Sarcoma

For localized sarcoma, limb-sparing resection with or without radiation forms

the backbone of treatment. Studies have evaluated chemotherapy in both the neoadjuvant and adjuvant settings, with the vast majority of studies evaluating doxorubicin-based chemotherapy regimens in the adjuvant settings. Due to the rare nature of sarcomas, most studies are not sufficiently powered to detect significant benefit from chemotherapy. Several trials evaluating chemotherapy regimens in the neoadjuvant and adjuvant settings needed to be terminated prematurely due to inadequate enrollment into the study.^{35,36}

For stage IA (T1a-Tb, N0, M0, low grade) tumors, no additional therapy is recommended after limb-sparing surgery with appropriate surgical margins. For stage IB (T2a-2b, N0, M0, low grade) tumors with insufficient margins, re-resection and radiation therapy should be considered, while for stage IIA (T1a-1b, N0, M0, G2-3) tumors preoperative or postoperative radiation therapy is recommended.² Studies have not found benefit of adjuvant chemotherapy in these low-grade, stage I tumors in terms of progression-free survival and overall survival.³⁷

• At what stage should chemotherapy be considered?

For stage IIB and stage III tumors, surgery and radiation therapy again form the backbone of therapy; however, neoadjuvant and adjuvant chemotherapy are also recommended as considerations. Anthracycline-based chemotherapy with either single-agent doxorubicin or doxorubicin and ifosfamide in combination are considered first-line chemotherapy agents in locally advanced STS.^{2,29,37}

Evidence regarding the efficacy of both neoadjuvant and adjuvant chemotherapy regimens in the setting of locally advanced high-grade STS has been mixed. The Sarcoma Meta-analysis Collaboration evaluated 14 trials of doxorubicin-based adjuvant chemotherapy and found a trend towards overall survival in the treatment groups that received chemotherapy.³⁷ All trials included in the meta-analysis compared patients with localized resectable soft-tissue sarcomas who were randomized to either adjuvant che-

motherapy or no adjuvant chemotherapy after limb-sparing surgery with or without radiation therapy. None of the individual trials showed a significant benefit, and all trials had large confidence intervals; however, the meta-analysis showed significant benefit in the chemotherapy treatment groups with regard to local recurrence, distant recurrence, and progression-free survival. No significant difference in overall survival was found.³⁷ Pervais et al updated the Sarcoma Meta-analysis Collaboration's 1997 meta-analysis with the inclusion of 4 new trials that evaluated doxorubicin combined with ifosfamide and found that both patients who received doxorubicin-based regimens or doxorubicin with ifosfamide had significant decreases in distant and overall recurrences. Only the trials that utilized doxorubicin and ifosfamide had an improved overall survival that was statistically significant (hazard ratio 0.56 [95% CI 0.36 to 0.85]; $P = 0.01$).²⁹ Although no significant heterogeneity was found among the trials included in either meta-analysis, a variety of sarcomas were included in each clinical trial evaluated. Given the extremely small number of each sarcoma subtype present in each trial, subgroup analysis is difficult and prone to inaccuracies. As a result, it is not known if certain histological subtypes are more or less responsive to chemotherapy.³⁷⁻³⁹

One randomized controlled trial evaluated neoadjuvant chemotherapy in high-risk sarcomas defined as tumors greater than 8 cm or grade II/III tumors. This study evaluated doxorubicin and ifosfamide and found no significant difference in disease-free and overall survival in the neoadjuvant therapy group compared to the control group.³⁵ There remains controversy in the literature with regards to adjuvant chemotherapy. Many oncologists offer adjuvant chemotherapy to patients with certain stage III subtypes. Examples of subtypes that may be offered adjuvant therapy include myxoid liposarcomas, synovial sarcomas, and leiomyosarcomas.² With regards to how many cycles of chemotherapy should be considered, a noninferiority study compared 3 cycles of epirubicin and ifosfamide to 5 cycles of epirubicin and ifosfamide in patients

➤FOR STAGE IIB AND STAGE III TUMORS, SURGERY AND RADIATION THERAPY AGAIN FORM THE BACKBONE OF THERAPY; HOWEVER, NEOADJUVANT AND ADJUVANT CHEMOTHERAPY ARE ALSO RECOMMENDED AS CONSIDERATIONS.

➤ IN AN ANALYSIS OF 1041 PATIENTS WITH STS OF THE EXTREMITIES, HIGH GRADE WAS THE MOST IMPORTANT RISK FACTOR FOR DISTANT METASTASES.

with high-risk locally advanced adult STSs. Three cycles of preoperative epirubicin and ifosfamide was found to be noninferior to 5 cycles with regards to overall survival.³⁸

• **What is this patient's risk for recurrence?**

The patient is at intermediate risk for recurrence. Numerous studies have demonstrated that tumor size, grade, and location are the most important factors to determine risk of recurrence, with larger size, higher grades, and deeper locations being associated with higher risk of recurrence. In an analysis of 1041 patients with STS of the extremities, high grade was the most important risk factor for distant metastases.³⁹

The highest risk of recurrence is within the first 2 years. Given that the patient's initial tumor was located in the extremity, he is more likely to have a distant metastasis as his site of recurrence; individuals with retroperitoneal tumors and visceral tumors are more likely to recur locally.⁴⁰ For STSs of the extremity, distant metastases determine overall survival, whereas patients with retroperitoneal sarcomas can die from complications of local metastases.⁴¹ Once a patient develops distant metastases, the most important prognostic factor is the size of the tumor, with tumors larger than 10 cm having a relative risk of 1.5 (95% CI 1.0 to 2.0).³⁹

• **What are the recommendations for surveillance?**

Surveillance recommendations are based on the stage of the sarcoma. Stage I tumors are the least likely to recur either locally or distally. As a result, it is recommended that stage I tumors be followed with history and physical exam every 3 to 6 months for the first 2 to 3 years, and then annually after the first 2 to 3 years. Chest x-rays should be considered every 6 to 12 months.² For stage II–IV tumors, history and physical exam is recommended every 3 to 6 months for the first 2 to 3 years. Chest and distant metastases imaging should also be performed every 3 to 6 months during this time frame. For the next 2 years, history and physical exam and imaging are recommended every 6 months. After

the first 4 to 5 years, annual follow-up is recommended.²

A study that followed 141 patients with primary extremity STSs for a median interval of 49 months found that high-grade tumors were most likely to recur during the first 2 years, with 20% of their patients recurring locally and 40% recurring distally. Chest x-rays performed during surveillance follow-up found distant lung metastases in 36 asymptomatic patients and had a positive predictive value of 92%, a negative predictive value of 97%, and a quality-adjusted life-year of \$30,000.^{40,41} No laboratory testing was found to aid in detection of recurrence.

➤ CASE CONTINUED

The patient does well for 1 year. With physical therapy, he regains most of the strength and coordination of the lower extremity. He is followed every 3 months with chest x-rays and a MRI of the thigh for the first year. On his fourth follow-up clinic visit, he describes increased dyspnea on exertion over the previous few weeks and is found to have multiple lung metastases in both lungs on chest x-ray. He undergoes further evaluation for metastases and is not found to have any other metastatic lesions. Bronchoscopy and biopsy of 1 of the lung nodules confirms recurrent dedifferentiated liposarcoma.

• **Should this patient undergo metastectomy?**

An analysis of 3149 patients with STS treated at Memorial Sloan-Kettering who developed lung metastases found that patients with pulmonary metastases have survival rates of 25%. The most important prognostic factor for survival was complete resection of all metastases.⁴² For stage IV disease, surgery is used only in certain instances. In instances where tumor is more localized or limited, removal of metastases or metastectomy can play a role in management.²

➤ CASE CONTINUED

Because the patient's metastases are limited to the lungs, he is referred for metastectomy. He undergoes wedge resection for definitive diagnosis but it is not possi-

ble to completely resect all of the metastases. He is thus referred to a medical oncologist to discuss his treatment options.

• What are treatment options for unresectable or metastatic disease?

METASTATIC DISEASE

Unlike local and locally advanced disease, chemotherapy forms the backbone of treatment in stage IV disease. Doxorubicin and olaratumab or doxorubicin and ifosfamide in combination are considered first line in metastatic disease. Response rates for single-agent doxorubicin range from 16% to 27%, while phase 2 and phase 3 studies of doxorubicin and ifosfamide have found response rates ranging from 18% to 36%.⁴³ In addition, the effectiveness of doxorubicin and ifosfamide phase 2 and 3 trials varied. Edmonson et al found a tumor regression rate of 34% for doxorubicin and ifosfamide as compared to 20% for doxorubicin alone.⁴⁴ In comparison, Santoro et al found a response rate of 21.3% for doxorubicin alone and 25.2% for doxorubicin and ifosfamide.⁴⁵ Neither study found increased survival benefit for doxorubicin and ifosfamide when compared to doxorubicin alone. In a Cochrane review evaluating randomized trials that compared doxorubicin and combination chemotherapy regimens, response rates varied from 14% for doxorubicin in combination with streptomycin to 34% for doxorubicin and ifosfamide. Most trials did not show a significant benefit for combination therapies when compared to doxorubicin alone.⁴³ Mean survival with doxorubicin or doxorubicin and ifosfamide is 12 months. High rates of recurrence highlight the need for additional chemotherapy regimens.

The newest approved agent is olaratumab, a monoclonal antibody that binds platelet-derived growth factor receptor alpha and prevents receptor activation. A phase 1-b and phase 2 trial evaluated patients with locally advanced and metastatic STS and randomly assigned them to either olaratumab and doxorubicin or doxorubicin alone.⁴⁶ Progression-free survival for olaratumab/doxorubicin was 6.6 months (95% CI 4.1 to 8.3) compared to

4.1 months (95% CI 2.8 to 5.4) for doxorubicin alone. The objective response rate was 18.2% (95% CI 9.8 to 29.6) for olaratumab/doxorubicin compared to 7.5% (95% CI 2.5 to 6.6) for doxorubicin alone. Furthermore, the median overall survival for olaratumab plus doxorubicin was 26.5 months (95% CI 20.9 to 31.7) compared to 14.7 months for doxorubicin alone (95% CI 5.5 to 26.0). Impressively, this improved response was notable across histological types. Furthermore, patients who had previously been treated with more than 1 regimen and those who were treatment naïve had similar response rates.⁴⁶

• What are second-line treatment options?

Doxorubicin has been used in combination with several other agents including dacarbazine (DTIC) as well as DTIC and ifosfamide (MAID). Borden et al evaluated patients with metastatic STS and randomly assigned the patients to either doxorubicin or doxorubicin and DTIC. Combination therapy demonstrated better tumor response than doxorubicin alone: 30% complete or partial response for combination therapy and 18% for doxorubicin alone.⁴⁷ However, Omura et al found similar rates of efficacy between doxorubicin and combination doxorubicin and DTIC in women with recurrent or nonresectable uterine sarcomas.⁴⁸ MAID has never been directly compared in a randomized trial to doxorubicin alone. In a study that compared MAID to doxorubicin and DTIC (AD) in patients with unresectable or metastatic sarcomas, MAID had superior response rates (32% versus 17%), but there was no difference with regards to overall survival (mean survival of 12.5 months).⁴⁹

Several additional regimens have undergone evaluation in metastatic and recurrent STSs. Gemcitabine has been used both as a single agent and as part of combination therapy in many studies. Studies with gemcitabine in combination with either docetaxel or DTIC have been the most efficacious. In a phase 2 trial, patients with metastatic STS were randomly assigned to either gemcitabine alone or gemcitabine and docetaxel. Combination therapy had a higher response rate (16% versus 8%) and longer overall survival

➤COMBINATION
THERAPY
DEMONSTRATED
BETTER TUMOR
RESPONSE THAN
DOXORUBICIN
ALONE: 30%
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FOR COMBINATION
THERAPY AND 18%
FOR DOXORUBICIN
ALONE.

➤GIVEN THE RARITY OF SARCOMAS AS A WHOLE, MANY TRIALS HAVE HAD DIFFICULTY RECRUITING ADEQUATE NUMBERS OF PATIENTS TO HAVE SUFFICIENT POWER TO DEFINITELY DETERMINE IF THE TREATMENT UNDER INVESTIGATION HAS CLINICAL BENEFIT.

(17.9 months versus 11.5 months) than gemcitabine alone.⁵⁰ Furthermore, a phase 2 trial of gemcitabine and docetaxel in patients with unresectable leiomyosarcoma showed an overall response rate of 56%, with 3 complete and 15 partial responses among the 34 patients enrolled in the study.⁵¹

A phase 2 trial randomly assigned patients with unresectable or metastatic STS to either DTIC or combination gemcitabine and DTIC.⁵² Gemcitabine-DTIC had a superior progression-free survival at 3 months (56% [95% CI 43% to 69%]) as compared to DTIC alone (37% [95% CI 23.5% to 50%]). Furthermore, mean progression-free survival and overall survival were improved in the gemcitabine-DTIC group (4.2 months and 16.8 months) as compared to the DTIC group (2.0 months and 8.2 months).⁵² DTIC has a single-agent response rate of 16%, but has been shown to be particularly effective in the setting of leiomyosarcomas.⁴⁹

• Does response to treatment regimens differ by histologic subtype?

The majority of STS trials include many different histologic subtypes. Given the rarity of sarcomas as a whole, many trials have had difficulty recruiting adequate numbers of patients to have sufficient power to definitely determine if the treatment under investigation has clinical benefit. Furthermore, the patients recruited have been heterogeneous with regard to subtype. Many older studies hypothesized that the efficacy of chemotherapeutic agents vary based on histologic subtype; however, for most subtypes the number of individuals included in those trials was too low to evaluate efficacy based on subtype.

Some exceptions exist, however. For example, both gemcitabine-DTIC and gemcitabine-docetaxel have been found to be particularly effective in the treatment of leiomyosarcomas.^{50,52} Additionally, a retrospective study found a 51% overall response rate for patients with myxoid liposarcomas treated with trabectedin.⁵³ Studies of patients with angiosarcoma treated with paclitaxel have demonstrated response rates of 43% and 53%.^{54,55}

• What are the newest approved and investigational agents?

A recently approved agent is trabectedin, a tris tetrahydroisoquinoline alkaloid isolated from ascidians that binds to the minor groove of DNA and causes disruptions in the cell cycle. Samuels et al reported data from a single-arm, open-label expanded access trial that evaluated patients with advanced metastatic sarcomas.⁵⁶ In this study, patients with liposarcomas and leiomyosarcomas had an objective response rate of 6.9% (95% CI 4.8 to 9.6) as compared to a rate of 5.9% (95% CI 4.4 to 7.8) for all assessable patients. Median survival was 11.9 months for all patients, with improved median survivals for liposarcoma and leiomyosarcomas of 16.2 months (95% CI 14.1 to 19.5) compared to 8.4 months (95% CI 7.1 to 10.7 months) for other subtypes.⁵⁶

Schöffski et al evaluated eribulin, a chemotherapeutic agent that affects microtubule dynamics, in a phase 2 trial of patients with progressive or high-grade STS with progression on previous chemotherapy. They found a median progression-free survival of 2.6 months (95% CI 1.7 to 6.2) for adipocytic sarcoma, 2.9 months (95% CI 2.4 to 4.6) for leiomyosarcoma, 2.6 months (95% CI 2.3 to 4.3) for synovial sarcoma, and 2.1 months (95% CI 1.4 to 2.9) for other sarcomas.⁵⁷

Van der Graaf and colleagues randomly assigned patients with metastatic nonadipocytic STS to pazopanib or placebo in a phase 3 trial. Pazopanib is a small-molecule endothelial growth factor inhibitor with activity against vascular endothelial growth factors 1, 2, and 3 as well as platelet-derived growth factors. Median progression-free survival was 4.6 months (95% CI 3.7 to 4.8) with pazopanib compared to 1.6 months (95% CI 0.9 to 1.8) with placebo.⁵⁸ Adipocytic sarcomas (liposarcomas) were excluded from the trial because phase 2 trials had found a lower rate of progression-free survival (26%) for them compared to other subtypes.

• What are the most common toxicities associated with the approved and investigational chemotherapeutic agents?

Toxicities were seen with each of the regimens studied and were common in the

randomized trials, with higher rates of toxicities in the combination chemotherapy regimens. The most common toxicities are myelosuppression, nausea, and vomiting. In the doxorubicin trials, the most common toxicities were myelosuppression, nausea, and vomiting.⁴⁴

Ifosfamide both as an individual agent and in combination with doxorubicin has higher rates and higher grades of toxicity than doxorubicin alone. Myelosuppression is the most common toxicity associated with ifosfamide, and the most commonly affected cell line is leukocytes.⁴⁴ Combination doxorubicin and ifosfamide also had high rates of nausea and vomiting (95%) and alopecia (100%).³⁵

Neutropenia is the most common toxicity associated with gemcitabine and dacarbazine, while their most common nonhematologic toxicities are fatigue and nausea.^{52,59} Trabectedin's most common toxicities are nausea (29%), neutropenia (24%), and fatigue (23%). It has also been shown to cause increased alkaline phosphatase (20%) and alanine aminotransferase (19%) levels.⁵⁶ In a phase 2 study of eribulin, 50% of patients had neutropenia, and other toxicities included fatigue, alopecia, nausea, sensory neuropathy, and thrombocytopenia.⁵⁷ Pazopanib is generally well tolerated; the most common toxicities are fatigue (65%), diarrhea (58%), nausea (54%), and hypertension (41%).⁵⁸ Higher rates of neutropenia, mucositis, nausea, vomiting, diarrhea, and transfusion reactions were seen with olaratumab and doxorubicin compared to doxorubicin alone in phase 1b and 2 studies.⁴⁶

► CASE CONTINUED

Given his poor prognosis with unresectable metastatic undifferentiated liposarcoma, the patient considers a clinical trial prior to undergoing combined therapy with doxorubicin and ifosfamide. He tolerates therapy well with stable disease at 6 months.

CONCLUSION

STSs are a heterogeneous collection of rare tumors. Low-grade, localized tumors have the best prognosis, and patients who undergo complete resection have the best

long-term survival. Due to the rarity of STSs, trials often have limited enrollment, and little progress has been made with regards to treatment and survival rates for metastatic and unresectable disease. All patients should be evaluated and treated at specialized sarcoma centers. This case highlights the need for continued research and clinical trials to improve overall survival of patients with sarcoma. **TSJ**

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► ALL PATIENTS SHOULD BE EVALUATED AND TREATED AT SPECIALIZED SARCOMA CENTERS. THIS CASE HIGHLIGHTS THE NEED FOR CONTINUED RESEARCH AND CLINICAL TRIALS TO IMPROVE OVERALL SURVIVAL OF PATIENTS WITH SARCOMA.

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Bilateral chylothorax in an AIDS patient with newly diagnosed Kaposi sarcoma

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DISCLOSURES

The authors report no disclosures or conflicts of interest.

Kaposi sarcoma is an angioproliferative tumor that is associated with human herpes virus-B (HIV-B). Mucocutaneous disease is the most common site for manifestation of AIDS-related Kaposi sarcoma, commonly affecting the lower extremities, oral mucosa, face, and genitalia. Pleural effusions can occur in 36%-60% of patients with Kaposi sarcoma, and it has been documented that chylothorax is a rare, but plausible presentation in patients with Kaposi sarcoma.¹ We present here a case of bilateral chylothorax in a patient with AIDS-related Kaposi sarcoma.

CASE PRESENTATION AND SUMMARY

A 52-year-old MSM male with AIDS (CD4, <20 mm³; viral load, 58 copies/ml) presented to the emergency department with complaints of shortness of breath, productive cough, and diarrhea for 2 days prior to presentation. His medical history also included chronic obstructive pulmonary disease, coronary artery disease, and hyperlipidemia. The patient was not on HAART because of his history of noncompliance. The results of a chest X-ray and computed-tomography (CT) scan showed that the patient had bilateral pleural effusion and a spiculated 14-mm nodule in the left upper lobe. The patient underwent ultrasound-guided placement of a 12-French left-sided chest catheter, and a milky white fluid was aspirated from the left pleural space. Laboratory analysis of the pleural fluid confirmed an exudate with an elevated triglyceride level of 120 mg/dL (chylous, >110 mg/dL) indicating chylothorax.

On close physical examination, the patient was found to have multiple irreg-

ular plaques on the back and lower extremities. As described by dermatology, there was a violaceous indurated plaque on the left axillae, violaceous indurated plaques with superficial scale grouped on the left midlateral back, and hyperpigmented lichenified plaques and papules on bilateral shins, with some with plate-like scale. Two punch biopsies were taken of the skin lesions, which confirmed Kaposi sarcoma, plaque stage from the lesion biopsied on the back, and patch stage from the lesion biopsied in the left axilla. Cytology of the pleural fluid was negative for malignant cells. On review by the radiologist of the CT scan of the chest, there was no indication of gross distention of the thoracic duct. Treatment options were offered to the patient, and the patient was considering options for chemotherapy and home hospice given his advanced disease state at the time of discharge.

DISCUSSION

Chylothorax occurs with a thoracic duct obstruction, which results in leakage of lymphatic fluid into the pleural cavity. The two leading causes of chylothorax are trauma and malignancy, with lymphoma being the most common cause of chylothorax among those with malignancy.² Chylothorax, however, is a rare but documented complication of Kaposi sarcoma. Marais and colleagues reported the case of a 3-year-old HIV-positive patient with newly diagnosed Kaposi sarcoma who was found to have tumor infiltration in the thoracic duct leading to bilateral chylothorax.³ Maradona and colleagues described a 40-year-old man with AIDS-related Kaposi sarcoma who was found to have pleural and pericardial Ka-

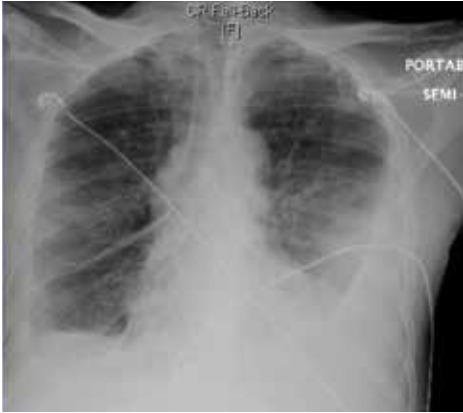


FIGURE 1. Chest X-ray showing bilateral pleural effusion blunting the costophrenic angles.

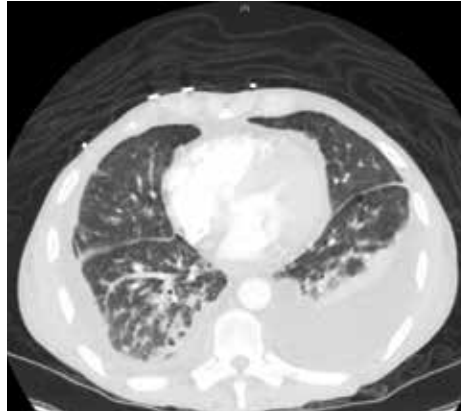


FIGURE 2. A helical computed-tomography scan of the chest showed bilateral pleural effusion.

posi sarcoma with chylothorax.⁴ Priest and colleagues wrote about a 32-year-old patient with AIDS with biopsy-proven Kaposi sarcoma who required multiple therapeutic thoracenteses for rapidly recurrent left chylothorax effusions.⁵

There are two leading discussions as to the pathophysiology of chylothorax that is related to Kaposi sarcoma: chylothorax developing secondary to metastatic disease or the development of chylothorax secondary to primary Kaposi sarcoma arising from the pleural region.⁶ One case report examined pleural and lung biopsies in a 34-year-old patient with AIDS-related Kaposi sarcoma that showed immunohistochemical staining that was suggestive of early-stage Kaposi sarcoma of lymphatic endothelial origin. The authors were attempting to illustrate that Kaposi sarcoma may have a stem-cell origin which can differentiate into lymph cells. Kontantinopoulos and colleagues postulated that in situ Kaposi sarcoma can arise from the lymphatic system with a resultant clinical presentation of chylothorax.⁷ The more mainstream thought however, is that chylothorax has been found to develop secondary to metastatic disease. The present case, therefore, illustrates an unusual presentation of cytology nega-

tive chylothorax in a patient with AIDS-related Kaposi sarcoma. **TSJ**

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► **CHYLOTHORAX, HOWEVER, IS A RARE BUT DOCUMENTED COMPLICATION OF KAPOSI SARCOMA.**

Pulmonary sarcomatoid carcinoma presenting as a necrotizing cavitory lung lesion: diagnostic dilemma

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DISCLOSURES

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Pulmonary sarcomatoid carcinoma (PSC) is a rare histological subtype that has an aggressive course with average survival of 11-13 months.¹ In clinical practice, the possible presentations of this rare cancer are not widely known, resulting in a misdiagnosis. That is what happened with our patient, who presented with necrotizing cavitory lung lesion and soft tissue necrotizing lymphadenitis. The clinical picture was reminiscent of tuberculosis or granulomatosis with polyangiitis and was further confounded by negative computed-tomography (CT)-guided biopsy and bronchoscopy findings, which added to the delay in diagnosis. With the currently available knowledge, the diagnosis of PSC depends largely on evaluation of the surgically resected specimen, which in most cases is avoided until there is a high suspicion of PSC. Biopsy is not useful due to extensive necrosis, as will be seen in our case. Consequently, most of the data in the literature is based on case series of autopsy specimen, and the clinical characteristics of PSC remain unclear. The rarity of PSC has prevented its characterization in literature. We report here a rare presentation of PSC with necrotizing lung lesion, to add to the paucity of the current data.

CASE PRESENTATION AND SUMMARY

A 58-year-old homeless man presented to the Upstate University Hospital, Syracuse, New York, with a 25-pound weight loss during the previous month and associated productive cough and hemoptysis for a week and a painful mass in the nape

of his neck. He denied any fever, chest pain, sick contacts, or joint pain. He had a history of about 40 pack-years of smoking, and his brother had recently been diagnosed with lung cancer. A tender fluctuant mass was detected in the nape of his neck on examination (**FIGURE 1**).

The patient had presented 9 months earlier with persistent cough and hemoptysis, and at that visit was found to have a cavitory lesion in the right lung measuring 2 cm (0.8 in). He had undergone a computed-tomography (CT)-guided biopsy of the lesion, which had shown acute and chronic inflammation with fibrosis, and he had negative bronchoscopy findings. The patient tested negative for tuberculosis during the first visit but he left the hospital against the medical advice of the physicians and he was lost to follow-up until his re-presentation.

On physical examination at his re-presentation, the patient seemed cachectic, with a blood pressure of 94/62 mm of Hg. The mass in the nape of his neck was about 3 cm (1.2 in) long, with erythema of the surrounding skin (**FIGURE 1**). Bronchial breath sounds were heard in the right upper lobe of the lung, likely due to the underlying cavitory lesion (**FIGURE 2B**). Relevant lab findings included a negative HIV test and repeat AFB (acid-fast bacilli) sputum cultures. A CT-guided biopsy with contrast of the thorax showed an interval increase in the size of the cavitory lesion in the patient's right upper lobe, now measuring about 10 cm (4 in). Also seen were multiple nodules elsewhere in both lungs, with the largest measuring 8 mm (0.3 in). A

CT scan of the neck showed 3 cm cystic mass within the posterior subcutaneous soft tissue of the C3 level, confirming the examination finding of the neck mass (**FIGURE 2A**) with peripheral enhancement and surrounding infiltrative changes, likely abscess or malignant lymph node versus necrotic infection. He underwent bronchoscopy, which again failed to reveal any endobronchial lesions. Bronchoalveolar lavage was sent for microbiological analysis, including AFB and fungus, but came back negative. Transbronchial biopsy cytology revealed fragments of tumor composed of large pleomorphic cells without glandular or squamous differentiation, within large areas of necrosis (Figure 3). Immunohistochemical studies showed strong reactivity with cytokeratin CAM5.2 (**FIGURE 4**), weak and focal reactivity with cytokeratin AE1/AE3 (**FIGURE 5**), and lack of reactivity with CD20, CD3, CD30, S-100, MART-1, TTF-1 and p63, all findings consistent with sarcomatoid carcinoma.

The patient underwent fine-needle aspiration and drainage of the neck lesion and the culture grew mixed organisms. The results of a bone scan, which was done within a week, showed multiple foci of uptake in the ribs and cervical spine. Given the patient's advanced disease, he was started on palliative radiotherapy with radiosensitizing chemotherapy with carboplatin (target AUC 6) and paclitaxel (135 mg/m² over 24 hours). His symptoms of hemoptysis improved transiently after the first cycle, but he became hypotensive and drowsy during the second cycle of therapy, and the family decided to make the patient comfort care and withdraw all further treatment. He was discharged to hospice.

DISCUSSION

PSC is a rare variant of non-small-cell carcinoma lung cancer, accounting for up to 0.4% of lung malignancy.¹ It was recently subtyped by the World Health Organization as a non-small cell lung carcinoma with certain amount of differentiation resembling sarcoma or containing elements of sarcoma.²⁻⁴ It is not known



FIGURE 1. Fluctuant mass, about 3 cm long, in the nape of the neck, after drainage, showing erythema of the surrounding skin.

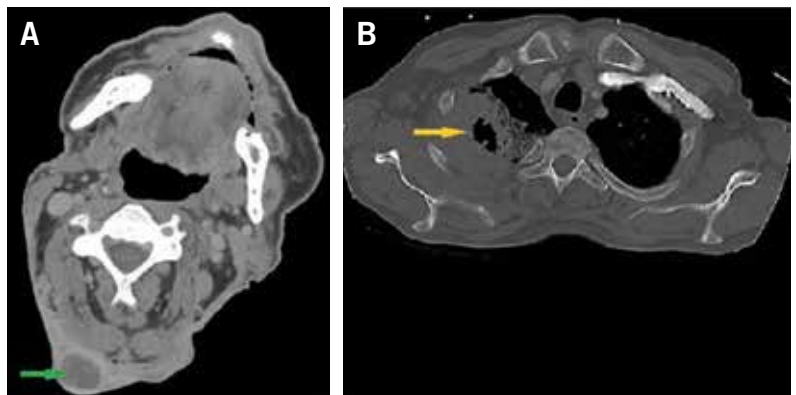


FIGURE 2. A, A computed-tomography scan of the neck, showing a cystic lesion in the posterior soft tissue (green arrow). B, A large necrotic cavity region in the right upper lobe of the lung (yellow arrow).

why both elements co-exist in the tumor, but Franks and colleagues some theories have been postulated in the literature, including possible origin from a single, aberrant stem cell with progenies differentiating in two separate pathways.³

Sarcomatoid carcinoma consists of spectrum of tumors including pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and blastoma.^{3,4} It usually shows male preponderance, and association with smoking.³ The diagnosis commonly occurs in the sixth decade of life, except for pulmonary blastoma, which is more common in the fourth decade and with equal gender distribution.⁴

The presenting symptoms can be variable and nonspecific, but predominantly include chest pain, cough, hemoptysis, and/or weight loss.⁵ Radiologically, pulmonary sarcomatoid cancer presenting

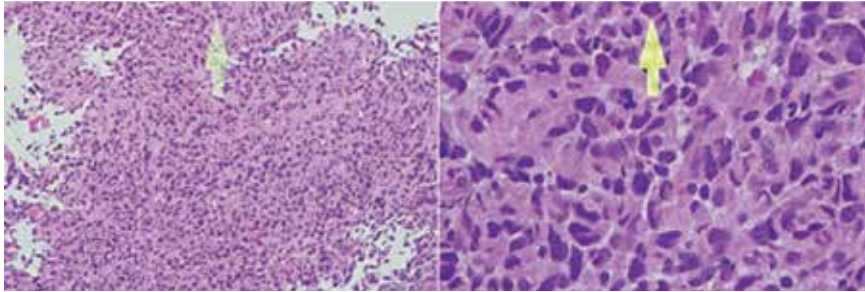


FIGURE 3. Images from the bronchoscopic biopsy, showing alveoli replaced by pleomorphic and spindle cells. Hematoxylin and eosin stain, x50 (left) and x200 (right). Arrows are artifacts from the microscope.

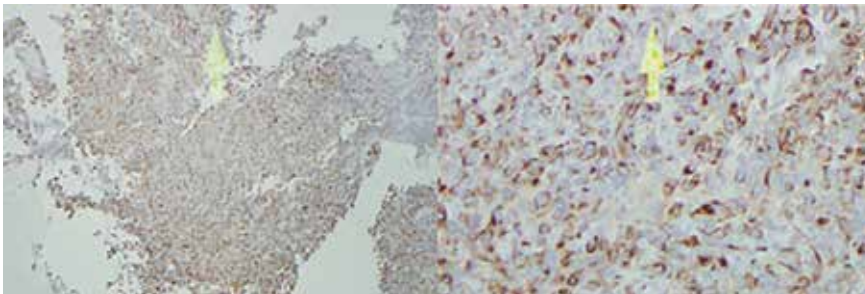


FIGURE 4. Biopsy tissue showing positivity to CAM 5.2. Hematoxylin and eosin stain, x200.

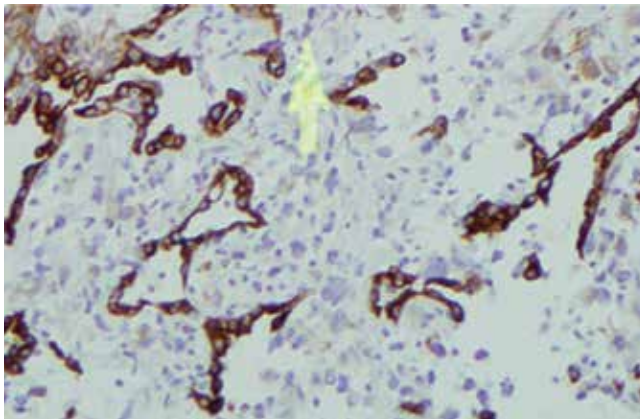


FIGURE 5. Biopsy sample showing focal reactivity to AE1/AE3. Hematoxylin and eosin stain, x200

as a necrotizing cavitory lesion in the lung is a rare finding, seldom reported in the past.^{6,7} The presentation in our case, with necrotizing lymphadenitis, was reminiscent of an infectious or autoimmune etiology such as tuberculosis or granulomatosis with polyangiitis. The presence of extensive necrosis in the lesion and the characteristic heterogeneity of the tumor had resulted in inconclusive biopsy findings during the previous presentation. In clinical practice, there is over-reliance on biopsy findings to make

the distinction between cancer and other mimicking conditions. This is especially true for rare tumors such as PSC, which often results in misdiagnosis and a delay in administering the proper treatment.

Transbronchial biopsy in cases such as the present case, carries little benefit because the diagnosis depends on the site from which the biopsy is taken and whether the biopsied tissue is representative of the entire mass. The diagnosis can be suspected based on the clinical and radiological findings but confirmation requires a surgical resection to delineate the accurate cytology and architecture.^{5,6,8} Huang and colleagues showed a misdiagnosis rate of PSC of >70% preoperatively.⁴ Resective surgery is feasible only in patients with high index of suspicion for a malignancy, which in most cases requires previous confirmation with a biopsy. The rarity of this cancer, its unusual presentations, and the lack of specific testing preclude early diagnosis and timely treatment of this fatal condition.

Initial treatment options for localized or with limited spread disease is resective surgery. The role of chemo- or radiation therapy is not known, but they have not previously shown promising results,^{6,8} except in some cases when they are used as postoperative adjuvant chemotherapy⁴ or in bulky, locally invasive tumors.¹ The recurrence rate after surgery is very high, resulting in a poor 5-year survival rate.^{1,8} Experimental therapies, such as antibodies that target epidermal growth factor receptor mutations, have not shown much success either.⁸ In conclusion, the outlook for patients with PSC with the current available knowledge and treatment protocols, is dismal.

Most of the current knowledge and data in the literature is based on cases from autopsy or early-stage surgical resections rather than on patients with advanced cancer.⁵ Moreover, the role of

surgical resection in PSC is questionable, given the high recurrence rate. Subsequently, the clinical and pathological manifestations have yet to be well characterized.⁴ There has been advance with the publication of more studies recently. Cytokeratin markers such as CAM 5.2 and AE1/AE3 are commonly useful to support the diagnosis when suspected.³ Other markers, including the carcinoembryonic antigen, CD15, and thyroid transcription factor-1 may be variably positive, based on the differentiation of the cancer. Other exciting prospects in the study of PSC include the suggestion of a modified vimentin histologic score for better characterization of the cancer and the discovery of high platelet-derived growth factor receptor beta immunohistochemistry expression in PSC as a potential target for future therapy.

CONCLUSION

Pulmonary sarcomatoid lung cancer can present with a predominant necrotizing picture that mimics diseases such as tuberculosis. In such case, transbronchial biopsy carries little benefit because the diagnosis depends on whether the biopsied tissue is representative of the entire mass, often confounded by the extensive necrosis. More data is needed to determine prognostic factors and appropriate therapeutic strategies.

TSJ

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