Soft-Tissue Sarcoma in Black Africans: Pattern, Distribution and Management Dilemma

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Background: Soft-tissue sarcomas (STS) are a heterogeneous group of rare tumors that arise predominantly from the embryonic mesoderm. Currently, >70 different histologic types of STS have been identified. There is no identifiable etiology in most cases of STS even though a variety of predisposing or associated factors have been identified. The American Cancer Society estimated that approximately 8,680 new cases were expected to be diagnosed, and 3,660 deaths in the United States were a result of STS in 2004. This study shows the pattern, distribution and problems of STS in a black African population.

Methods: We retrospectively reviewed 209 patients that were managed for STS between the periods of January 1985 to December 2004. Materials for the study were obtained from the case notes as well as the histopathology reports of the patients.

Results: Two-hundred-nine patients were treated for STS during the 20-year study period. The peak incidence of age occurred between the third and sixth decades of life with a slightly male preponderance. Fibrosarcoma was the commonest STS, followed by malignant fibrous histocytoma, liposarcoma and rhabdomyosarcoma. Fibrosarcoma, malignant fibrous histocytoma and liposarcoma are more common in the extremities while leiomyosarcoma is more common in the intra-abdominal region.

Conclusion: The treatment of STS is a multidisciplinary approach, and patients have benefited from multimodality treatment. In the western countries, STS most commonly present as asymptomatic masses with tumors in the distal extremities, often small in size when discovered. In our own environment, delayed and advanced stages of the disease are the rule. Modern imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are not commonly available—and where they are available, they are usually not affordable for the majority of our patients. We need to establish good interdisciplinary relationships among the managing physicians and educate our patients on early presentation to the hospital.

Key words: tumors ■ Africans ■ pattern

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INTRODUCTION

Soft-tissue sarcomas (STSs) are a heterogeneous group of rare tumors that arise predominantly from the embryonic mesoderm. According to American Cancer Society estimates, approximately 8,680 new cases were expected to be diagnosed and 3,660 deaths resulted from STS in the United States in 2004, accounting for 0.63% of all cases and 1.15% of deaths from cancer.[1] STS can occur anywhere in the body, but most originate in an extremity (59%), the trunk (19%).[2] Currently, >70 different histologic types of STSs have been identified, but the most common are malignant fibrous histocytoma (28%), leiomyosarcoma (12%), liposarcoma (15%), synovial sarcoma (10%) and malignant peripheral nerve sheath tumors (6%),[3] with rhabdomyosarcoma being the most common STS in children.

The pathogenesis of STS is not completely understood. External radiation therapy is a well-established risk factor for STS, as shown by the fact that the incidence of sarcoma is increased 8–50-fold in patients treated with radiation therapy for cancer of the breast, cervix, ovary, testes or lymphatic system[4,5] Chronic lymphedema following axillary dissection is another risk factor; the subsequent lymphangiosarcoma is known as Stewart-Treves syndrome. Some specific inherited genetic alterations have also been associated with an increased risk of both bone and STS.

In black Africans, there is paucity of information on STS. In Nigeria, the National Cancer Registry shows that this tumor is increasing in incidence.[6] This study was conducted to show the pattern and distribution of STS in a black African population at a tertiary institution as compared to what happens in the western world, and to discuss the problems encountered by the practi-

tioners in this part of the world. This will serve as a stimulus to the practitioners in the developing countries on the challenges involved in the current multidisciplinary and multimodal treatment of patient with STS.

PATIENTS AND METHODS

This study took place at a tertiary health institution that has a 450-bed space. It serves the entire people of its state of location and ≥4 other neighboring states with an estimated population of 10.5 million people. We retrospectively reviewed 209 patients that were managed for STS for a period of 20 years (January 1985 to December 2004). Materials for the study were obtained from the case notes as well as the histopathology reports. Patients variables analyzed included the age, sex, histology types, site of tumor and where available treatment given. Data collected was analyzed with a computer using SPSS® 10.0 to generate frequency tables.

RESULTS

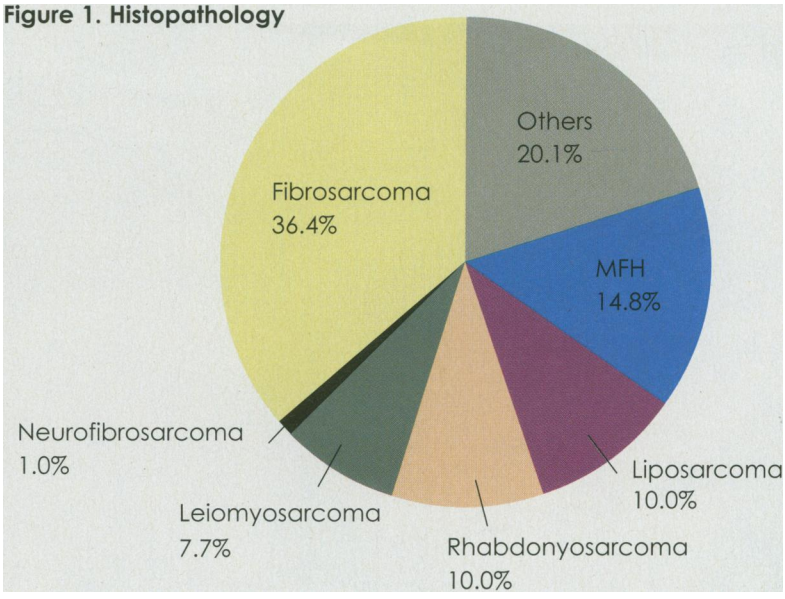
Two-hundred-nine patients were treated for STS during the 20-year study period. The age range is as shown in Table 1 with the peak incidence occurring between the third and the sixth decades of life, which constitute about 67.5% of the total population. There was slightly more male preponderance, with 55% being male and 45% female. Figure 1 shows different histologic types obtained in this part of the world. Fibrosarcoma topped the list with 36.4% of the total patients diagnosed, followed by malignant fibrous histocytoma, liposarcoma and rhabdomyosarcoma. Other varieties of the STS constitute about 20%. These include dermatofibrosarcoma protuberance, which constitutes the bulk of it (it is a low grade of fibrosarcoma); Kaposi's sarcoma; angiosarcoma; granular cell tumor; synovial cell sarcoma; and undifferentiated malignant mesenchymal tumors. Table 2 shows that lower extremity is the most common site of STS, followed by the trunk in our environment. More than 50% of the rhabdomyosarcoma occurred in the younger group, aged <20 years. In the extremities, fibrosarcoma, malignant fibrous histocytoma and liposarcoma are more common, as shown in Table 2. Fibrosarcoma, malignant fibrous histocytoma and liposarcoma are uncommon in the intra-abdominal and retroperitoneal region, while leiomyosarcoma is more common in the intra-abdominal region. Though this study does not address details of clinical presentations, delayed and advanced stages of the disease are the rule in our environment, as shown in Figures 2 and 3.

DISCUSSION

Soft tissues are the extraskeletal tissues of the body that support, connect and surround other discrete anatomic structures. These tissues constitute >50% of the body weight, and include muscles and tendons as well as fibrous, adipose and synovial tissues. There is no identifiable etiology in most cases of STS. A variety of predisposing or associated factors have been identified.[7] Alteration in the important cell regulatory genes, p53 and Rb, are common and thus it is not surprising that inherited mutations of these genes in hereditary retinoblastoma and Li-Fraumeni syndrome confer a substantial risk for sarcoma.[8] Chemical herbicides and dioxin have been claimed to cause increased sarcomas in forestry workers and Vietnam veterans, but the data are conflicting.[9] Lymphedema is associated with lymphangiosarcoma, most often after radical lymphadenectomy but also with filariasis and congenital lymphedema.[10,11] Cytogenetic analysis of soft-tissue tumors has also identified distinct chromosomal translocations that code for oncoproteins associated with certain histologic subtypes. The best characterized gene rearrangements have been found in alveolar rhabdomyosarcoma (PAX3-FHKR fusion), clear cell sarcoma (EWS-ATFI fusion) and synovial sarcoma (SSX-SYT fusion).[12]

The result of this study showed that STS is more common in adults, with a male preponderance, as it has been reported by most western literature. The majority of our patients are within their third and sixth decades of life. Malignant fibrous histocytoma (18%), liposarcoma (20%) and leiomyosarcoma (19%) are said to constitute the majority of adult STS in the western countries.[13] Another study quoted malignant fibrous histocytoma as the most common tumor, accounting for 10–20% of all STS. This is closely followed by liposarcoma and then leiomyosarcoma.[14] This is, however, different from what we obtained from our center, where fibrosarcoma

Figure 1. Histopathology



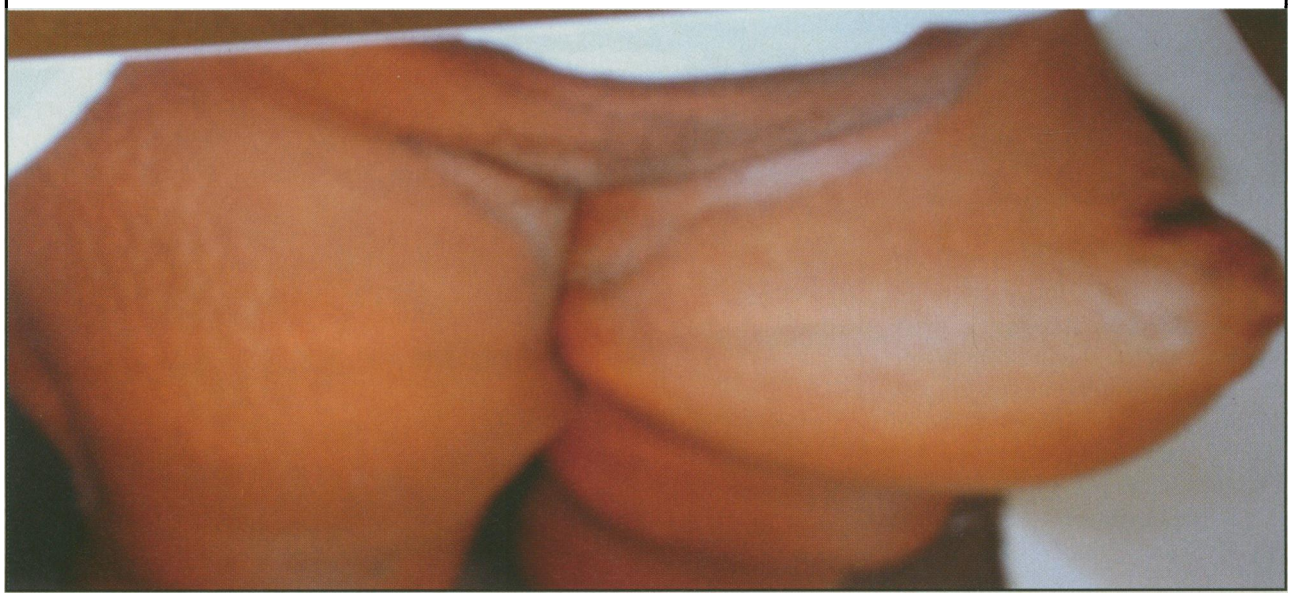
appeared to be the most common of the malignant soft-tissue tumor. It constitutes 36.4% of the total tumor, followed by malignant fibrous histocytoma (14.8%), leiomyosarcoma (10%) and rhabdomyosarcoma (10%). Other tumors constitute 20.1%, of which dermatofibrosarcoma protuberance constitutes the majority. Though controversial, it is a variant of fibrosarcoma but of a very low grade. Other tumors in this group includes Kaposi's sarcoma, angiosarcoma, granular cell tumor, synovial cell sarcoma and undifferentiated malignant mesenchymal tumor. Our study showed that fibrosarcoma, malignant fibrous histocytoma and liposarcoma are common in the extremities, while in the intra-abdominal and retroperitoneal region, fibrosarcoma, malignant fibrous histocytoma and liposarcoma are uncommon. Leiomyosarcoma is, however, common in the intra-abdominal region. These findings are similar to the results obtained in the western world.[13,15] STSs most commonly present as asymptomatic masses. It is said that the size of the mass at presentation usually depends on the location of the tumor and that tumors in the distal extremities are often small when discovered, while tumors in the proximal extremities and retroperitoneum can become quite large before they are apparent. These statements cannot be said for our patient in this part of the world. From our personal experience in our center, apart from some cases of dermatofibrosarcoma protuberance that presented much earlier, most of the extremities tumors present later with a large tumor sometimes in the range of 15–30 cm in diameter. Examples of such presentation are shown in Figures 2 and 3. This is a very serious problem for the practitioners in this part of the world. The late presentations are due to ignorance and poverty.

Table 1. Soft-tissue sarcoma in black Africans: pattern, distribution and management dilemma

	Age Distribution	
Age Range	**Frequency**	**Percent**
Valid		
0–9	15	7.2
10–19	19	9.1
20–29	26	12.4
30–39	44	21.1
40–49	40	19.1
50–59	32	15.3
60–69	25	12.0
≥70	8	3.8
Total	209	100.0

On the issue of diagnosis, the use of fine-needle aspiration biopsy or even the Tru-cut biopsy does not arise in most of our patients. The lesions are usually very large, and most of them will require incisional biopsy. The exceptions are some cases of dermatofibrosarcoma protuberance that present early and therefore will have an excision biopsy. When incisional biopsy is done by the primary attending physician, the biopsy incision is poorly orientated, which will subsequently affect the definitive wide local excision. Axially oriented incision biopsy is recommended to make wide local excision possible later. Pretreatment radiological imaging is critical in defining the local extent of a tumor, staging the disease and aiding in diagnosis. Each imaging modality, however, has a particular place in patients with STS. In our environment, we are seriously handicapped to the varieties of imaging modality that are available and affordable to our patients. We always request for the plain radiograph of the affected part to exclude underlying bony involvement, especially in extremity lesions, as shown in Figure 4. Chest radiogra-

Figure 2. Myxoid liposarcoma in a 38-year-old female



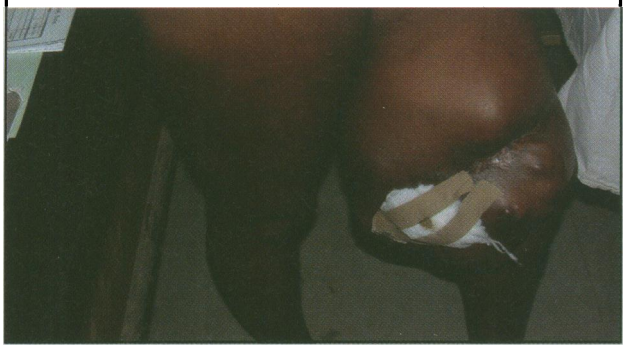
phy is also routinely performed to look for lung metastases even though we know that computed tomography (CT) of the chest is the best for patients with high-grade lesions or tumors >5 cm. CT is also the preferred imaging technique for evaluating retroperitoneal sarcomas.[16] CT is not readily available in most tertiary centers and where it is available it may not be affordable. It costs about ₦40,000.00 (U.S. $400) to do a CT in Nigeria, where the gross domestic product per capita is U.S. $320. Magnetic resonance imaging (MRI) is the preferred imaging modality for extremity sarcoma because it can accurately delineates muscle groups and distinguishes bone, vascular structures and tumors.[17,18] This is not available in most centers and where it is, it is not mostly affordable to our patients. We do not even think of magnetic resonance angiography (MRA) because we are still far from it. However, in our center, for extremity sarcoma, vascular angiography is done before the main surgical excision. This has been able to guide our dissection with respect to the adjacent vascular structures. We also routinely request abdominal/pelvic ultrasonography, not only for intra-abdominal tumors but also for extremity tumors to look for evidence of metastasis to the liver. Intravenous urography (IVU), barium enema, or barium meal and endoscopy may be requested in suspected cases of visceral sarcoma. The current American Joint Committee on Cancer (AJCC) staging criteria for STS relies on certain parameters. These include the histologic grade of the tumor (G), the size (T) and the presence of distant (M) or nodal metastases (N).[19] The histologic grade of STS remains the most important prognostic factor. To accurately determine the tumor grade, in addition to special staining technique, you need an experienced sarcoma pathologist. This is another major dilemma in developing countries such as ours. Most STS slides are read by general pathologists and in almost all cases, the tumors are never graded. It is, however, known that sarcomas may be misdiagnosed or misclassified by the general pathologist in up to 25–40% of cases.[20,21] The size of the STS is another important prognostic variable. Sarcomas have classically been stratified into two groups on the basis of size; T1 lesion are ≤5 cm, and T2 lesions are >5 cm. Lesions ≤5cm even of high grade have limited risk of local or distant recurrence and should not be grouped with large high-grade lesions for treatment purposes. In our environment, the majority of the lesions are usually large, making the prognosis worse. Therefore, we find it very difficult to accurately stage the STS using the AJCC TNM staging. The tumors are usually not graded; they are of very large size, and there is no modern equipment such as CT and MRI readily available and affordable to pick evidence of distant or nodal metastases.

For the treatment of STS, a multidisciplinary approach is currently undertaken. Patients have benefited from multimodality treatment approach. The overall five-year survival rate in patients with STS of all stages remains only 50–60%.[22] Most patients die of metastatic disease, which becomes evident within 2–3 years of the initial diagnosis in 80% of cases.[15] Patients considered to have high risk of recurrence and death include those presenting with metastatic disease, localized sarcomas at sites other than the extremities or sarcomas >5 cm of intermediate or high histologic grade (T2).[23,24] Surgery remains the main potentially curative therapy for STS. The type of surgical resection is determined by several factors, including tumor location, tumor size and the depth of invasion, the involvement of nearby structures, the need for skin grafting or autogenous tissue reconstruction, and patient's performance status. Currently, the role of adjuvant radiotherapy has gradually been defined, allowing evolution of treatment from a situation where amputation was the standard treatment, to the present time where limb-sparing surgery is appropriate in >90% of patients with extremity STS.[25] Wide local excision is the primary treatment strategy for extremity sarcomas, with the goal to resect the tumor with a 2–3-cm margin of surrounding normal tissue. This is very difficult to achieve in our environment because of the large size of the tumor at presentation. Radiotherapy can be used for situations where the sarcoma is not amenable to surgical excision. When used as the primary treatment, large doses are needed, and the control rate is 30–60%.[26] Adjuvant radiotherapy after surgical excision improves local control.[27] There has been extensive debate over the role of adjuvant chemotherapy. Doxorubicin hydrochloride is the agent most frequently used, usually in combination with other drugs such as dacarbazine, cyclophosphamide and, more recently, ifosfamide.[28] Meta-analysis of the published

Table 2. Soft-tissue sarcoma in black Africans: pattern, distribution and management dilemma

	Tumors					
Sites of the Tumor	Head & Neck	Lower Extremity	Upper Extremity	Trunk	Intra-Abdo.	Retrop.
Malignant fibrous histocytoma	7	12	2	3	7	
Liposarcoma	2	9	1	3	4	2
Leiomyosarcoma	1	2	1	1	11	
Fibrosarcoma	6	33	9	22	4	2
Rhabdomyosarcoma	6	7	3	3	2	
Total	22	63	16	32	28	4

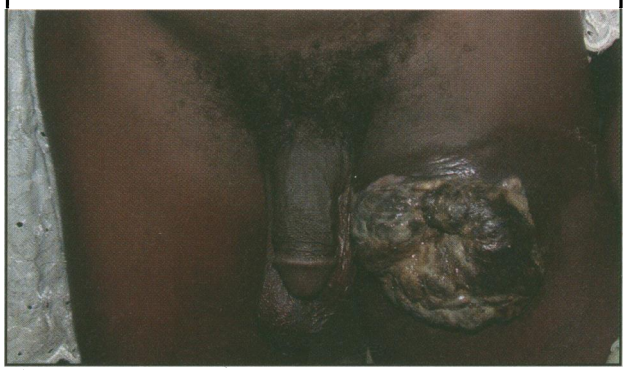
Figure 3. Fibrosarcoma in a 32-year-old woman



reports suggested that postoperative adjuvant chemotherapy significantly improves the overall and disease-free survival for those with large (>5 cm) high-grade sarcoma.[29]

In developing countries such as ours, a multidisciplinary approach to the treatment of patients with STS is still in the infancy stage and so also the multimodality treatment. The interaction between the primary physicians at the primary and secondary health centers with their counterpart at the tertiary center is poorly developed. Even at the tertiary center, the interaction among the surgical oncologist, the pathologist, the radiotherapist, the radiologist and the chemotherapist is far from being founded. If we must make headway in the treatment of patients with STS in this part of the world, there must be an organized interdisciplinary interaction. Our patients need to be educated on early presentation if we are to achieve positive tumor-free margins postexcision. Centers in which they have radiotherapist must be seriously linked up for proper and adequate postoperative radiotherapy. We must also encourage the management of our tertiary institution to make available and at affordable prices the drugs used as adjuvant chemotherapy. Gastrointestinal sarcomas present with symptoms similar to those of carcinomas from the same organ, and the diagnosis is often made at laporatomy. Surgical resection with adjuvant chemotherapy has been advocated. A lot of research has been done in the developed countries in the understanding of the molecular characteristics of these tumors. Our priority is, however, different in developing countries. We need to equip our histopathological unit with enough equipment and reagents so that they are able to grade the tumor with respect to their degree of cellularity, differentiation, pleomorphism and necrosis as well as the number of mitoses. Some of our pathologists should be encouraged to take more interest in sarcomas with the aim of becoming a experienced sarcoma pathologist. If we can have our tumor graded and patients present early, then we shall be able to grade and prognosticate the outcome of management of patients with STS. Very soon, we hope to embark on a multicenter study in the management of these patients. With this, we shall be able to have a large series and come out with specific data on the patient's response to surgical excision pre- or postoperative radiotherapy, chemotherapy, year of survival as well as the disease-free interval as we have in the developed countries.

Figure 4. Ulcerated fibrosarcoma in a 28-year-old male



In conclusion, management of STS in the developing countries is still a serious dilemma partly because of the late presentation of our patients and largely because of nonavailability of some modern equipment to adequately and appropriately manage these patients. However, within the limit of the available resources, we need to establish a good interdisciplinary relationship among managing physicians and to educate our patients on early presentation to the hospital when they notice a mass of 5 cm in diameter or any new mass that persists for >4 weeks.

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