Uterine sarcomas in South African black women: a clinicopathologic study with ethnic considerations

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Summary

Background: There is considerable evidence for a higher incidence of uterine sarcomas in blacks when compared to whites. However, whether this higher incidence is related to differences in clinicopathologic presentation is not known.

Patients and Methods: We reviewed slides and clinical charts of 81 patients with a primary diagnosis of uterine sarcoma referred between 1991 and 1999 to Kalafong Academic and Pretoria Academic Hospital. After review, 49 cases remained for study.

Results: Uterine sarcomas were distributed between leiomyosarcoma (LMS) (39%), carcinosarcoma (CS) (49%) and endometrial stromal sarcoma (ESS) (12%). LMS and ESS tend to present at an earlier age when compared to CS (respectively $p < 0.008$ and 0.02). Of women with LMS more women are premenopausal when compared to CS ($p < 0.009$). Lower abdominal pain is more common in LMS ($p < 0.009$), whereas bleeding is more common in women suffering from CS ($p < 0.01$). Lymphovascular space involvement and cervical involvement are more common in CS when compared to LMS. In CS, the carcinoma component has most of the metastatic potential.

Conclusion: Among black South African women different clinicopathologic features for uterine LMS, CS and ESS are observed. We also present genetic and/or hormonal factors possibly contributing to the pathophysiology of uterine sarcomas in blacks.

Key words: Uterine sarcoma; Leiomyosarcoma; Carcinosarcoma; Endometrial stromal sarcoma; Race; Ethnic.

Introduction

At least in some cancers, ethnicity-related variation in primary tumor biology has been suggested. Prostate cancer presents as a more advanced disease and recurs more frequently among young African-American men [1] and a large increase in incidence of proximal colon carcinoma among blacks has been reported [2]. Black women present at younger age and with more advanced stage of breast carcinoma [3] . Black women show a proportionately fewer number of endometrial adenocarcinomas than whites [4] and tend to have more advanced disease at the time of diagnosis and a higher proportion of undifferentiated endometrial carcinomas [5].

Uterine sarcomas (UTS), comprising leiomyosarcoma (LMS), carcinosarcoma (CS) and endometrial stromal sarcoma (ESS), account for only 3% of uterine malignancies [6]. The etiology of UTS is largely unknown, treatment modalities disappointing and prognosis is poor, even for stage I disease [7]. Although most studies reported on UTS mainly concern white women, there is considerable evidence for a higher incidence of UTS in American blacks [4, 8-12]. However, we are not aware of the clinicopathologic data in this subgroup. We therefore present a retrospective analysis of clinical and pathologic data of uterine sarcomas in South African black patients. We also address hormonal and genetic aspects possibly underlying ethnic differences.

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Patients and Methods

Clinical samples

From 1991 through 1999 a total of 81 black patients were diagnosed as having UTS at the Pretoria Academic Hospital and Kalafong Academic Hospital. After reviewing available histologic material by two of the authors (FA and LD), a total of 49 tumors qualified for inclusion in the study. Reasons for exclusion are presented in Table 1. The number of paraffin blocks per case ranged from 3 to 44 blocks with a mean of 17.5 blocks per patient and a mean of 10.5 blocks of the tumor. In each case, the following clinical data were tabulated: age of patient, parity, menopausal status, history of pelvic irradiation, symptoms, duration of symptoms, and primary treatment. Macroscopic morphologic features that were tabulated in each case: length of uterus, diameter of tumor, macroscopic necrosis, omental involvement and organ resection. Microscopic morphologic features that were tabulated in each case: endometrial status, LMS originating from leiomyoma, presence of lymphovascular space infiltration, presence and type of necrosis, hypercellularity, atypia, mitotic index, presence of abnormal mitotic figures, epithelioid differentiation, myxoid differentiation and evaluation of tumor border as infiltrative or circumscribed. The following were considered (singly or in combination) to represent cytologic atypia: nuclear hyperchromatism, nucleomegaly, prominent nucleoli and irregular nuclear membranes. Groups were labeled using a two-tiered scheme of "insignificant atypia" (none to mild) or "significant atypia" (moderate to severe). The surrounding normal myometrium was taken as a reference and the same scheme was used to label cellularity. Mitotic figures were counted in the mitotically most active areas. A randomizing strategy that involved starting in the field with a mitotic figure or figures and then moving to another contiguous field in an unpremeditated way was used. At least four sets of 10 high-

Table 1. — *Reasons for exclusion at the time of pathological review. Values are given as n (%).*

	LMS	CS
Mitotically active LM	18 (22)	
Insufficient viable tissue	4 (5)	2 (2)
Retroperitoneal LMS	2 (2)	
No slides available	2 (2)	
Vaginal LMS	1 (1)	
Pure rhabdomyosarcoma		1 (1)
Endometrial adenocarcinoma		1 (1)
Atypical LM	1 (1)	

LMS: leiomyosarcoma; CS: carcinosarcoma; LM: leiomyoma.

power fields were counted using a x40 objective and x10 ocular. Of the four sets, the highest counts were used. Only unequivocal mitotic figures were scored. Mitotic index was not counted in CS. LMS was diagnosed according to the Stanford criteria [13] and the degree of cytologic atypia, mitotic index and the presence or absence of coagulative tumor cell necrosis (CTCN) was assessed. CTCN was thus distinguished from hyalin necrosis, ulcerative necrosis and hemorrhage [13]. In contrast to hyalin necrosis, CTCN features an abrupt transition from the viable tumor cells to the necrotic cells. As a result smooth muscle tumors were differentiated as leiomyoma with increased mitotic index, atypical leiomyoma and leiomyosarcoma. The carcinomatous and sarcomatous elements of each CS were examined separately according to well established criteria [6]. The carcinoma was typed as endometrioid adenocarcinoma, squamous carcinoma, serous papillary carcinoma, clear cell carcinoma or undifferentiated. None of the tumors contained mucinous carcinoma. The sarcomatous component of each tumor was also analyzed separately. Presence and types of malignant heterologous elements (rhabdomyosarcoma, chondrosarcoma, fibrosarcoma and melanocytic) were noted in each case. None of the tumors contained osteosarcoma or liposarcoma. The spindle cell component was classified as homologous i.e. leiomyosarcoma or nonspecific sarcoma. The primary antibodies used for this analysis were as follows: anti-human cytokeratin (MNF116), anti-epithelial membrane antigen (EMA), anti-vimentin, antimyoglobin, antidesmin and anti-muscle specific actin. In eight cases diagnosis of the rhabdomyosarcoma component was made on clear and unequivocally morphologic features only, but without immunohistochemical stainings. Rhabdomyoblasts are characterized by abundant eosinophilic cytoplasm, an eccentrically located nucleus and cross-striations can be seen. In case of lymphovascular space (LVS) infiltration and metastasis, the infiltrative component was identified. Pure sarcomas were excluded. ESS were subdivided into low grade ESS (LG-SS) and high grade ESS (HG-SS) according to well established criteria [6]. The mitotic index of ESS was not used as a criterion. The number of leiomyomas was described as "few" when there were 2 or 3 and as "multiple" when there were ≥ 4.

Patients were retrospectively staged according to a modified staging system of the International Federation of Gynecologists and Obstetricians (FIGO) for endometrial cancer, but without subdividing stage I into IA and IB. We derived staging information from pathology reports and our review.

Follow-up information was recorded including progression-free interval, site of recurrence and treatment for recurrence. However, this information was regarded as non representative since only five (10%) had a follow-up of more than six months.

Statistical analysis

Statistica TM (Statsoft) was used and comparison of the three subtypes was performed by analysis of variance (ANOVA) where appropriate. The chi-square test was used for comparison of categorical outcomes where applicable, Fisher's exact test was used when the expected value in any of the cells was less than 5. The α-level was set at 0.05.

Results

Uterine sarcoma

Of the 49 cases considered to be uterine sarcomas, 19 (39%) were classified as LMS, 24 (49%) as CS and six (12%) as ESS. Stage distribution was as follows: 35% stage I, 8% stage II, 24% stage III, 23% stage IV and unknown stage in 10%. Overall, analysis of variance (ANOVA) gives a p-value for age < 0.0088, indicating that significant differences between subtypes exist. Information regarding a history of pelvic irradiation was available in 32 (65%), but none of them ever received pelvic radiotherapy. Distribution of symptoms and clinical signs was as follows: bleeding in 36 (73%), lower abdominal pain (LAP) in 21 (43%), enlarged uterus in 13 (26%), mass protruding through cervical os in 12 (24%), constipation in four (8%), urinary complaints in three (6%), deep venous thrombosis in one (2%), weight loss in one (2%), ascites in one (2%) and grade IV dyspnea in one (2%). Thirteen women (26%) presented with one symptom only. Primary treatment consisted of biopsy in six (12%); total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) in 31 (63%); TAH, BSO and omentectomy in nine (18%); TAH in two (4%) and a vaginal hysterectomy in one (2%). Macroscopic features of UTS were a mean uterine length of 13 cm (SD 4.6) and a mean largest diameter of the tumor of 10 cm (SD 5.1). Comparison of the mean largest tumor diameter of the three subtypes showed no significant differences ($p < 0.14$).

Leiomyosarcoma

Forty-seven cases with a primary diagnosis of LMS were evaluated. Twenty-eight cases were excluded (Table 1) and 19 cases remained for study. An overview of the most significant clinical features is presented in Table 2. There was no difference in age at presentation between

Table 2. — *Comparison of clinicopathologic features of the uterine sarcoma subtypes. Values are given as % unless otherwise indicated.*

	LMS	CS	ESS
Age (yrs)	57	65	54.7
Premenopausal	37	4	33
Nulliparous	5	0	
Symptoms*	3.5 (3.4)	4.5 (5.8)	
Stage I	26	29	83
II	5	12.5	0
III	26	25	17
IV	32	21	0
Unknown stage	10	12.5	0

*mean duration in months (SD).
LMS: leiomyosarcoma; CS: carcinosarcoma; ESS: endometrial stromal sarcoma.

Table 3. — *Comparison of the most important symptoms in leiomyosarcoma (LMS) and carcinosarcoma (CS) among blacks. Values are given as n (%).*

	LMS (n = 19)	CS (n = 24)	p=value*
Vaginal bleeding	10 (53)	21 (87)	0.014
Low abdominal pain	14 (74)	7 (29)	0.009
Mass through cervix	3 (16)	8 (33)	NS
Enlarged uterus	6 (32)	6 (25)	NS

LMS: leiomyosarcoma; CS: carcinosarcoma; NS: not significant.
* Chi-square test.

Table 4. — *Association of leiomyomas with leiomyosarcoma (LMS) and carcinosarcoma (CS) ($p < 0.28$, Chi-square test). Values are given as n (%).*

	LMS (n = 19)	CS (n = 24)
None	5 (26)	11 (46)
One, "few" or "multiple"	11 (58)	9 (37.5)
Unknown	3 (16)	4 (17)

LMS and ESS ($p < 0.59$) but both present at an earlier age when compared to CS (0.008 and 0.019 are respectively the p-values). When compared to CS, more women suffering from LMS are premenopausal ($p < 0.009$, Fisher's exact). Distribution of parity for LMS is as follows: P_0=1 (5%), $P_{1\text{-}2}$=5 (26%), $P_{3\text{-}5}$=6 (32%), $P_{6\text{-}8}$=5 (26%), $P_{\geq 9}$=1 (5%) and unknown parity=1 (5%). Distribution of symptoms is summarized in Table 3. In addition, obstipation was present in two (10%), urinary symptoms in one (5%), deep venous thrombosis in one (5%) and weight loss in one (5%). Only four women had only one complaint (21%). Primary treatment consisted of TAH and BSO in 12 cases (63%); TAH, BSO and omentectomy in three cases (16%); TAH in two cases (10%) and a vaginal hysterectomy in one case (5%). In one case (5%) only a biopsy was taken and in two cases (10%) intestinal resection was part of the debulking procedure.

Mean uterine length was 14.6 cm (SD 5.7) and mean tumor diameter was 12.5 cm (SD 4.8). The association between uterine LM and LMS is presented in Table 4. No LMS seemed to originate from a leiomyoma. Lymphovascular space (LVS) involvement was detected in seven (37%) (Table 5) and CTCN was seen in 16 (84%). Cellularity was classified as insignificantly increased in two (10%) and as significantly increased in 17 (90%). Atypia was classified as insignificant in one (5%) and as significant in 18 (95%). Mean mitotic index was 26/10 HPF (SD 18); abnormal mitotic figures were present in 17 (89%). We noted one case of epithelioid and one case of myxoid LMS. In all cases where the myometrial/tumoral border could be evaluated (74%), it was infiltrative. Distribution of metastatic disease is given in Table 5.

Carcinosarcoma

Twenty-eight cases with a primary diagnosis of CS were reviewed. Four cases were excluded (Table 1); 24 cases remained for study. Some clinicopathologic features are presented in Table 2. Distribution of parity was as follows: $P_{1\text{-}2}$=8 (33%), $P_{3\text{-}5}$=10 (42%), $P_{6\text{-}9}$=4 (17%) and unknown parity in 2 (8%). Distribution of symptoms and clinical findings are summarized in Table 3. In addition, an abdominal mass was palpable in six (25%), obstipation was present in two (8%) and urinary complaints in two (8%). Only five (21%) had only one symptom. Primary treatment was as follows: TAH and BSO in 14 (58%); TAH, BSO and omentectomy in five (21%) and biopsy in five (21%).

Mean uterine length was 12.1 cm (SD 4.3) and mean diameter of the tumor was 8.1 cm (SD 4.8). Association between uterine LM and CS is presented in Table 4. Some microscopic features are presented in Table 6. We could not discriminate between homologous and heterologous in four (17%) because of a poorly differentiated sarcomatous component in three and because of insufficient tissue (biopsy) in one. Necrosis was seen in 21 (87.5%). Cellularity and atypia were quoted as significant and abnormal mitoses were present in all cases where evaluation was possible (96%). An overview of LVS infiltration, metastatic spread and the infiltrative component is presented in Table 5. LVS infiltration was noted in 17 (71%), absent in four (17%) and in three (12%) evaluation was not possible. There was a tendency for LVS involvement to be more common in CS when compared to LMS; however, the difference was not statistically significant ($p < 0.5$).

Endometrial Stromal Sarcoma

Six patients with a primary diagnosis of ESS were reviewed and none was excluded. One study case was reclassified as HG-SS instead of LG-SS. Five (83%) were thus classified as HG-SS and one (17%) as LG-SS. Some clinicopathologic features are shown in Table 2. Symptoms and clinical signs at presentation were distributed as follows: vaginal bleeding in five, mass protruding through cervical os in one, enlarged uterus in one and ascites in one. TAH and BSO was performed as a primary treatment in 5/6 cases and an additional omentectomy was performed in one case. Mean length of the

Table 5. — *Lymphovascular space (LVS) infiltration and metastatic spread in leiomyosarcoma and both components of carcinosarcoma. Absolute numbers are given. Different sites of metastasis can occur in the same patient.*

		Carcinoma (n = 24)	
	Leiomyosarcoma (n=19)	Sarcoma component	Carcinoma component
LVS*	7	2[§]	13[§]
Adnexal	4		6
Cervix	1		4
Parametrium			1
Omentum	2	2[†]	3[†]
Intestine	2		1
Lymph nodes	2		1
Peritoneal			1
Pulmonary			1

* $p < 0.5$ (Chi-square test) for comparison of LVS infiltration between LMS and CS; [§] in 2 cases of CS we could not discriminate between the two components; [†] 2 cases were biphasic.

Table 6. — *Microscopic features of carcinosarcoma (CS) in blacks. Values are given as n (%).*

Type of carcinoma	
endometrioid adenocarcinoma	19 (79)
undifferentiated	3 (12)
serous papillary	1 (4)
squamous component*	5 (21)
clear cell component*	1 (4)
unspecified	1(4)
Type of sarcoma	
heterologous	17 (71)
rhabdomyosarcoma	11 (46)
chondrosarcoma	1 (4)
rhabdo- and chondrosarcoma	4 (17)
melanotic- and rhabdomyosarcoma	1 (4)
homologous	3 (12)
leiomyosarcoma	2 (8)
homologous NOS	1 (4)
NOS	4 (17)

NOS: not otherwise specified; * in combination with endometrioid adenocarcinoma.

uterus was 12 cm (SD 0.75) and mean maximal diameter of the tumor was 8.5 cm (SD 4.9). Necrosis was present in 50% and haemorrhage in one case. Uterine leiomyomas were associated in only one case. LVS infiltration was noted in five cases, whereas necrosis was present in four. Cellularity was classified as significant in all cases, whereas atypia was classified as insignificant in one (17%) and significant in five (83%). Mitoses were only present in HG-SS. Mean mitotic index was 24.2 (SD 15) and abnormal mitotic figures were noted in all cases.

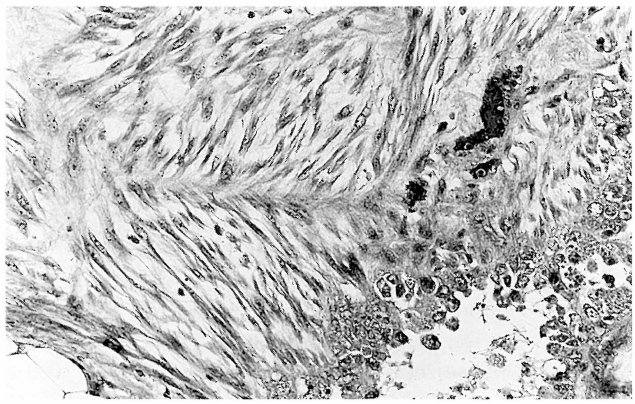
Discussion

There is considerable evidence for a higher incidence of UTS in blacks when compared to whites [4, 8-12]. The etiology of UTS is largely unknown, but genetic or hormonal factors might contribute to the pathophysiologic mechanisms. UTS have complex karyotypic abnormalities [14-16], showing both numerical and structural abnormalities. However, clonal chromosome changes also have been described [17, 18]. Whether cytogenetic differences between blacks and whites exist is not known, but ethnic differences on a molecular genetic level have been described. The presence of the CYP1A1 MspI site-present allele, which was found to be associated with Japanese lung cancer risk, was statistically increased in African compared to Caucasian Americans [19]. The nuclear enzyme poly(ADP-ribose) polymerase (PADPRP) is thought to play a role in DNA recombination, replication and repair and its polymorphism may provide a valid marker for a predisposition to multiple myeloma, prostate and lung cancer in black individuals [20, 21]. The c-myc proto-oncogene is associated with cellular proliferation and its inappropiate expression may be involved in carcinogenesis and in tumor progression [22]. In cervical cancer c-myc gene overexpression was more likely in African than in European women and was related to risk of relapse, irrespective of the other prognostic factors [23]. Overexpression of the p53 tumor suppressor gene is described in UTS [24-27] and seems to be more common in CS than in LMS [27]. Whether loss of functional p53 because of mutation and/or deletion of the p53 gene plays a role in the higher incidence of UTS among blacks has not been studied yet, but in endometrial adenocarcinoma p53 overexpression is more common among blacks [28] and is regarded as a possible factor contributing to the racial disparity in survival. Recently, loss of heterozygosity for chromosome 10 has been observed in uterine LMS [29]. PTEN (MMAC1) is a tumor suppressor gene on chromosome 10 [30] and is therefore also a good candidate for further study.

Epidemiological studies have indicated an etiological role for unopposed estrogens in uterine sarcoma [10, 12]. In general, African-American women appear to have higher levels of serum hormones than Caucasian women [31-34]. Evidence for hormone sensitivity of UTS arises from observational studies, case reports and animal studies. The risk of endometrial sarcoma appears to be increased by exogenous (hormone replacement therapy) or endogenous (thecoma, polycystic ovaries) conditions leading to unopposed estrogen stimulation of the uterus [35, 36]. Recently, an extremely fast tumor growth of a LMS during pregnancy has been described [37]. Some researchers were able to produce endometrial sarcomas in up to 15% of experimental animals being treated with combined estrogen and progesterone therapy [38]. The unopposed estrogenic action of tamoxifen might also be associated with occurrence of UTS. Indeed, LG-SS [39, 40] and CS [41-45] in patients receiving tamoxifen have been described. The evidence appears to be stronger for ESS and CS but LMS in a woman taking tamoxifen has been described [46]. The hypoestrogenic state resulting from long-term leuprolide acetate treatment causes similar vascular changes in leiomyosarcoma as were seen in leiomyoma. But in contrast to the histologic response, there was no clear clinical response [47, 48]. Whether the suggested hormone sensitivity of UTS combined with higher levels of serum hormones [31-34] can explain the increased incidence among blacks is not known. Ethnic hormonal differences are probably more important for the increased incidence of uterine leiomyomas among black women [49, 50] than UTS, however, their role has yet to be explored.

Black women with LMS and ESS present at an earlier age than CS (respectively $p < 0.008$ and 0.02) (Table 2) and this explains the higher percentage of premenopausal women in LMS when compared to CS ($p < 0.009$). Symptoms at presentation are different between LMS and CS (Table 3). Women suffering from LMS tend to present more often with lower abdominal pain ($p < 0.009$), whereas women suffering from CS tend to present with vaginal bleeding ($p < 0.014$). In this series of LMS the mean maximal tumor diameter was 12.5 cm (SD 4.8 cm). In probably mixed populations presenting with LMS,

Fig. 1



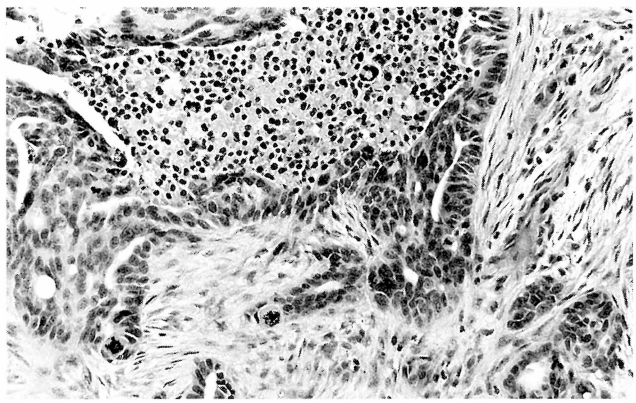


Fig. 2

Figure 1. — Herringbone pattern suggestive of fibrosarcomatous differentiation in the omentum. Hematoxylin and eosin (x400).
Figure 2. — The omental biopsy shows, apart from a necrotic area, mitosis in both the epithelial and sarcomatous component. Hematoxylin and eosin (x400).

more than 80% had a tumor size smaller than 10 cm in one study [51] whereas the mean tumor diameter was 6.5 cm in another report [52]. In addition, in the current report only 26% of patients suffering from LMS presented in stage I disease, compared to 53-55% in European whites [53-55]. One could easily argue that socioeconomic, cultural and religious factors contribute to a later diagnosis and thus a larger tumor diameter and higher stage in blacks. However, if this is the only explanation, one could expect that also CS is larger in blacks than in whites, but this does not appear to be the case. In this series 29% of women with CS presented in stage I, a figure resembling the findings in European whites [53, 55]. For CS among blacks, we could not confirm the younger age and more advanced disease compared with whites, as was suggested previously [56].

It is reported that the carcinoma component of CS has the greatest metastatic potential [57, 58]. Also in blacks it is the epithelial component of these tumors that mostly invades LVS and metastasizes (Table 5). Thus, regardless of race, it appears that CS behaves like poorly differentiated endometrial carcinomas, a theory supported by immunohistochemical studies [59]. However, the present study contains two cases of biphasic omental metastasis (Figures 1 and 2). The metastatic potential of the sarcoma component is confirmed by two cases of LVS infiltration by mesenchymal cells (Figure 3).

It is suggested that LMS and CS have a different metastatic spread pattern [51]. We did find a similar spread pattern for the two subtypes (Table 5), which is in concordance with autopsy studies [60, 61]. Adnexal involvement was relatively more common in LMS, which is probably due to the more advanced stage in our study group. Lymph node involvement cannot be compared since it was not systemically performed in our series.

Some reports have implicated prior radiation as a causative agent [11, 62]. In our series none of the patients ever received radiotherapy. Therefore, pelvic irradiation does not seem to play a major role in the pathogenesis of UTS among black women.

Exploring prognostic factors in this group would be very interesting, however, only in a minority of patients do we have data on follow-up. The majority of these patients are referrals from distant hospitals in rural areas where "witch" doctors (locally called "sangomas") function as primary health services. Patients therefore not only do not come for follow-up visits, but often do not get the proposed adjuvant treatment. This was a major drawback in our attempt to obtain data on disease-free survival and overall survival.

Our results demonstrate differences in the clinicopathological presentation of LMS, CS and ESS among South African black women. In general, the clinicopathologic findings are similar to the features observed in whites. The only different parameter might be a larger tumor diameter and resultant higher stage at presentation for LMS among blacks. In fact this is an intriguing observation since its benign counterpart also has been observed to occur more commonly, earlier and in more advanced stages in the black population [49, 50]. However, comparison to published studies of white European patients is inappropriate. Therefore, it seems interesting to compare the clinicopathologic findings of UTS in a population-based study.

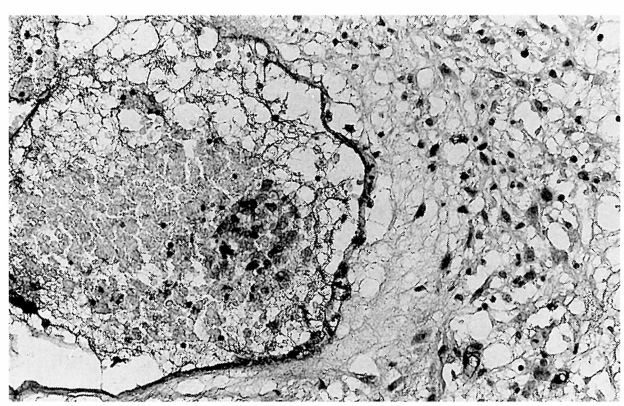


Figure 3. — Endothelial cell immunoperoxidase staining with Factor VIII related antigen (DAKO) shows vascular infiltration in a sarcomatous area. Hematoxylin and eosin (x400).

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