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Original Article

Clinicopathologic features of Stewart-Treves syndrome

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Abstract: Aims: To demonstrate clinicopathologic features of Stewart-Treves syndrome (STS) including clinical manifestations, morphology, immunophenotype (especially c-MYC amplification), differential diagnosis, pathogenesis, treatment and prognosis. Methods and results: 17 cases of STS were retrospectively archived, involving 6 cases of postmastectomy, 3 cases of postoperative cervical cancer and 8 cases of chronic lymphatic obstruction without history of malignancy. Seven of 9 cancer patients had undergone radiotherapy. All the patients presented with lymphedema as the first sign. The lesions appeared as multiple reddish blue macules or nodules with polypoid and coalesce. Microscopic examination revealed infiltrative proliferation of irregular vessels in dermis and subcutaneous tissue. The tumorous endothelial cells displayed pleomorphism in morphology. The heteromorphic tumor cells expressed CD34, CD31, ERG, D2-40, c-MYC and factor VIII. Despite various treatment modalities, all cases died in an average of 13.6 months, with 1 case of loss to follow-up. Conclusions: STS is an extremely rare malignancy that arises from congenital or secondary chronic lymphedema. STS uniquely overexpressed c-MYC. In spite of poor prognosis, early detection is important to facilitate a full range of available therapies, even an opportunity for curative treatment. A low threshold for biopsy and early referral to an experienced multidisciplinary team are highly recommended for optimum management.

Keywords: Lymphangiosarcoma, lymphedema, postmastectomy angiosarcoma, Stewart-Treves syndrome, c-MYC

Introduction

Angiosarcoma (AS) is a rare variant of highly aggressive sarcoma originated from vascular or lymphatic endothelial cells. Sixty percent of AS are cutaneous. Generally speaking, AS includes 2 subtypes: 1) primary/idiopathic cutaneous; 2) secondary comprised of post-irradiation and lymphedema-associated (Stewart-Treves syndrome, STS). Actually, Stewart and Treves first reported AS arising from long-standing lymphedematous extremities due to lymphedematous nodes dissection following a radical mastectomy, which was named as "Stewart-Treves syndrome" in 1948 [1]. STS is classically described in patients as mentioned above. In fact, the term "Stewart-Treves syndrome" can be broadly applied to a group of lymphangiosarcomas originated from either congenital or acquired chronic lymphatic obstruction [2]. Up to now, more than 400 cases of STS have been reported in English literature. Patients have very poor prognosis, complicated with recurrence, distant metastases, and death within 2 years [1, 3]. The prevalence of STS has been decreased on account of wide adoption of breast-conserving surgery and substantial improvement in techniques of radiation therapy. STS has been rarely described in the presence of idiopathic chronic lymphedema and postoperative cervical cancer. Herein we report 17 cases encountered in our practice to illustrate clinical presentation, disease progression, and prognosis of STS. Early detection of this deadly malignancy is critical to improve clinical outcome.

Material and methods

Patient selection

A total of 17 cases with STS were collected from January 1, 2012 to September 1, 2018 in the Capital Medical University Affiliated Beijing Shijitan Hospital (Beijing, China). The diagnosis was confirmed by 2 physicians independently

Table 1. Clinicopathologic characteristics of 9 STS cases with history of malignancy

Case ID	Age (y)	Sex	Localization	Previous Tumor	Treatment	Latency (y)	Duration of edema (y)	Follow-up (months)/Outcome
1	74	F	Left upper limb	L/BC	S1/RT/C	22	5	12/DOD
2	67	F	Right upper limb	R/BC	S1/RT/C	17	17	6/DOD
3	60	F	N/A	N/A	N/A	N/A	N/A	N/A
4	64	F	Right elbow	R/BC	S1/RT	14	10	5/DOD
5	62	F	Left upper limb	L/BC	S1/RT/C	13	13	12/DOD
6	43	F	Left upper limb	L/BC	S1/RT/C	14	13	28/DOD
7	58	F	Left leg	CC	S2/RT/C	22	22	12/DOD
8	47	F	Left lower extremity	CC	S2	10	10	31/DOD
9	60	F	Both lower extremities	CC	S2/RT/C	12	11	30/DOD

BC, breast cancer; C, chemotherapy; CC, Cervical cancer; DOD, died of disease; F, female; L, left; M, male; N/A, not available; R, right; RT, radiation therapy; S, surgery (1. Modified radicalmastectomy + axillary lymph node dissection; 2. Radical hysterectomy and pelvic lymphadenectomy).

Table 2. Clinicopathologic characteristics of 8 cases with chronic lymphatic obstruction

Case ID	Age (y)	Sex	Localization	Treatment	Recurrence/times	Duration of edema (y)	Follow-up (months)/ Outcome
10	63	M	Right lower limb	S1/RT/C	N	0.55	3/DOD
11	39	M	Left leg	S1/RT/C	N	25	10/DOD
12	66	F	Right leg	S1/RT	N	60	5/DOD
13	37	F	Left lower limb	S2/RT	Y/3	37	25/DOD
14	65	F	Left lower limb	S1/RT	N	20	4/DOD
15	23	M	Left upper limb	S2/RT/C	N	23	22/DOD
16	24	F	Left lower limb	S1/RT	Y/3	24	20/DOD
17	15	F	Left lower limb	S1/RT/C	Y/3	6	28/DOD

C, chemotherapy; DOD, died of disease; F, female; M, male; N/A, not available; R, right; RT, radiation therapy; S, surgery (1. Local resection, 2. Complete leg amputation).

after reviewing hematoxylin and eosin stained slides. The present study was approved by ethics committee of the Capital Medical University Affiliated Beijing Shijitan Hospital (Beijing, China). Each patient had provided written informed consent for inclusion.

Histology and immunohistochemistry

Resected surgical specimens were fixed in 10% phosphate-buffered, neutral formaldehyde solution at room temperature for 24 hours and dehydrated in an ascending series of ethanol. Samples were routinely embedded in paraffin, washed with xylene, rehydrated in a descending series of alcohol, washed with distilled water, and then stained with hematoxylin and eosin for 30 minutes, at room temperature. Sections (4-μm thick) were observed under a light microscope with the magnifications of ×40, ×100, ×200 and ×400, respectively.

Immunohistochemistry was performed per manufactory protocols using Ventana Automatic Immunohistochemistry Stainer for molecules as the following: CD34 (1:100, Dako, USA), CD31 (1:100, Zymed, USA), D2-40 (1:100, Dako, USA), CK-pan (1:60, Zymed, USA), EMA (1:60, Zymed, USA), HHV-8 (1:100, Zymed, USA), ERG (1:100, Dako, USA), C-MYC (1:25, Abcam, USA), β-catenin (1:100, Dako, USA), Vimentin (1:120, Dako, USA), factor VIII (1:50, Dako, USA) and Ki-67 (1:75, Dako, USA). The primary antibodies were replaced by PBS in negative controls. All Sections were counterstained with 3,3'-diaminobenzidine tetra-hydrochloride (DAB).

Cases were considered positive for CD34, CD31, D2-40, CK-pan, FVIII, EMA, β-catenin, or vimentin with the presence of membrane/intracytoplasmic immunoreaction, while for ERG or c-MYC with the presence of nucleus immunore-

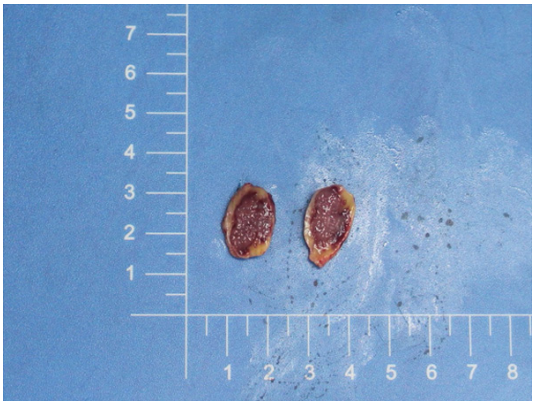

Figure 1. One case showed subcutaneous nodular gray-red mass with a diameter of 1.5 cm.

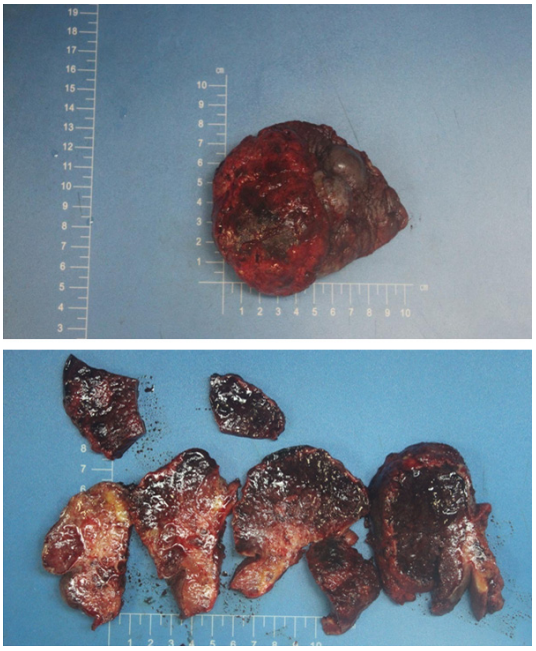

Figure 2. Another case showed subcutaneous irregular nodular soft mass, with a maximum diameter of 10 cm; the cut surface was dark-red, microcystic and spongy hemorrhagic.

action in tumor cells. Immunoreactivity for Ki67 was expressed as the percentage of tumor cells counted across three representative fields.

Results

Clinical features

Totally 545 patients with medical history of long-standing lymphedema were treated at Capital Medical University Affiliated Beijing

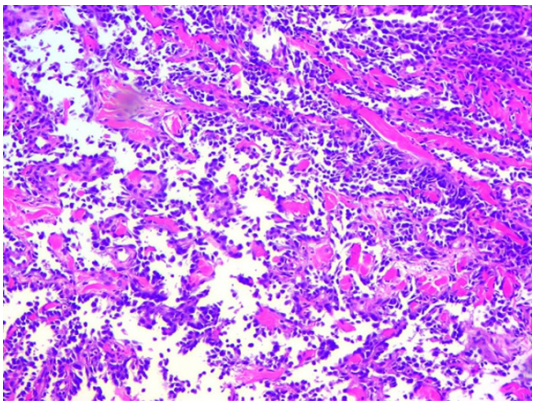

Figure 3. Different sizes and forms of irregular lumens scattered in the dermis and subcutaneous tissue, part of which communicate with each other, and take the shape of channel-like structure (H&E ×100).

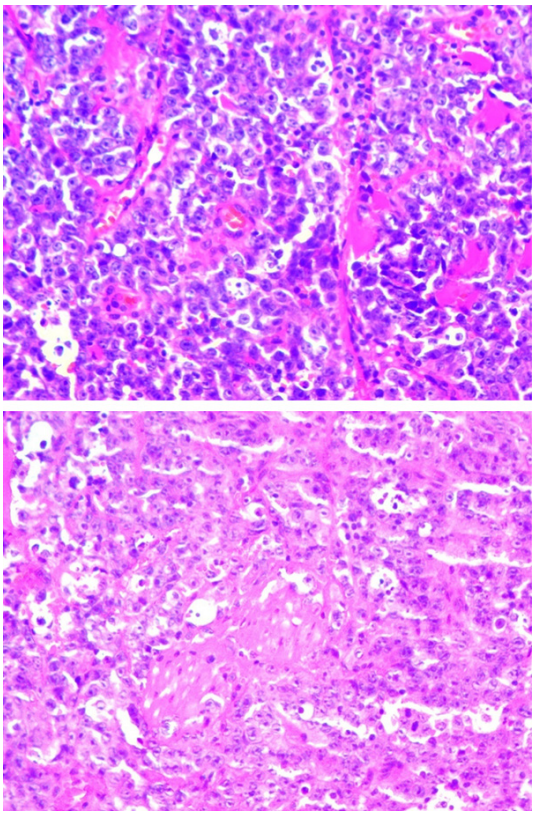

Figure 4. The tumor cells are arranged in a solid pattern, consisting of large epithelioid cells with pleomorphic nuclei and prominent nucleoli (H&E ×200).

Shijitan Hospital from 2012 to 2018. Seventeen cases of STS were retrieved, including14 females and 3 males, aged from 15 to 74 years (median: 51.1 years). Six cases had undergone radical surgery for breast cancer, 3 cases for

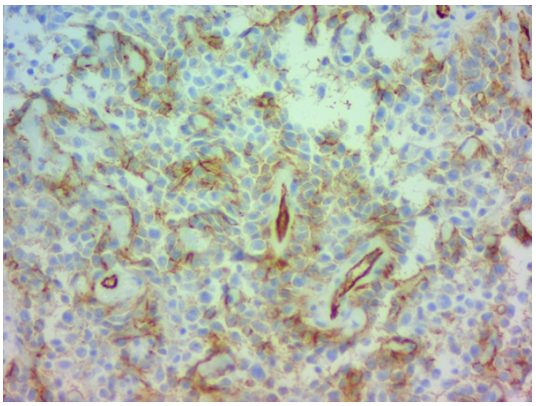

Figure 5. Positive expression of CD31 (IHC ×200).

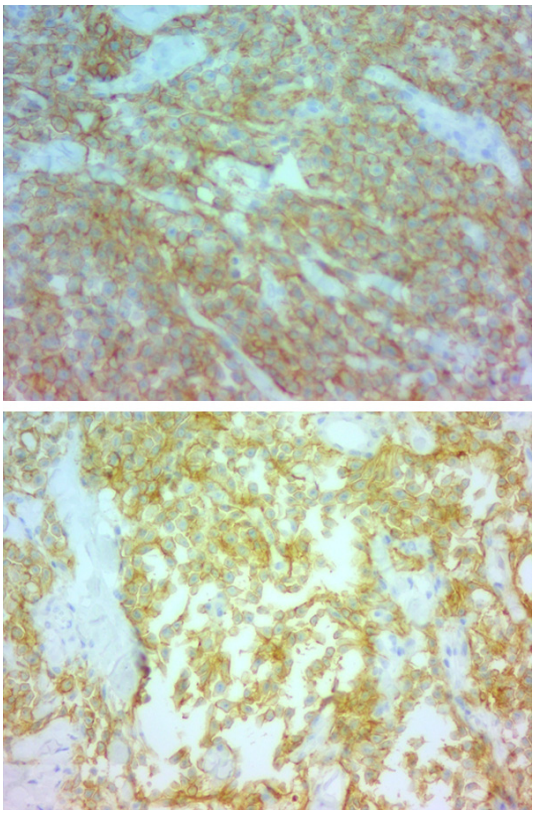

Figure 6. Positive expression of D2-40 in poorly and well differentiated areas (IHC ×200).

cervical cancer. Among 9 patients with malignancy, 7 had received radiation therapy. Eight cases were diagnosed with congenial lymphedema. One of them suffered from pulmonary metastasis in 6 months after diagnosis. Ten neoplasms were located in lower limbs, whereas 7 in upper limbs. Those lesions developed from non-irradiated areas. The main clinical

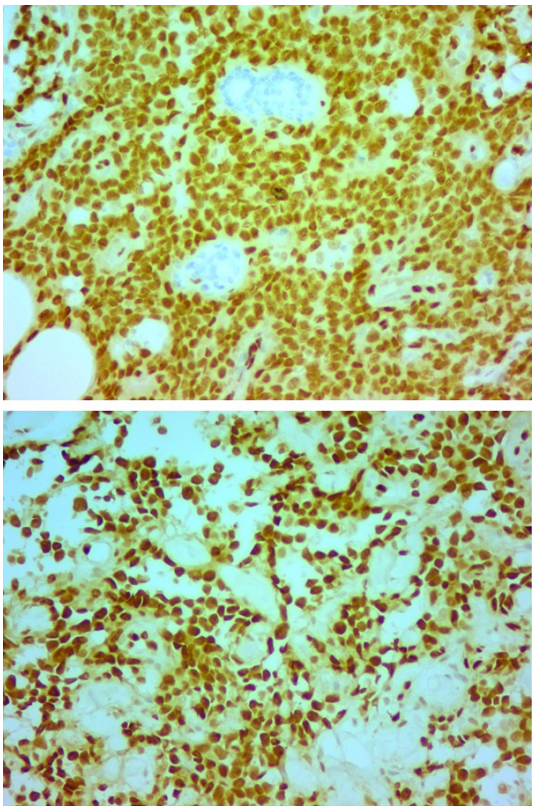

Figure 7. Strong positive expression of ERG in poorly and well differentiated areas (IHC ×200).

features in this series are summarized in **Tables 1**, **2**.

For the cases with post-irradiation lymphedema, STS could present as early as 5 years after onset of lymphedema (with an average of 13 years). Cases without primary malignancy (and consequently without history of radiation) demonstrated a much longer latency (with an average of 22.6 years) between the onset of lymphedema and the diagnosis of STS.

Gross appearance

All excisional specimens were skin and subcutaneous tissue, with the greatest diameter ranging from 1.3 to 9 cm. The skin surface was dark red or grayish-brown. 3 cases had skin ulceration. 4 cases had subcutaneous nodular masses with the maximum diameter of 0.8-2.0 cm (**Figure 1**). 9 cases presented as subcutaneous irregular masses, one typical case showed subcutaneous irregular nodular soft mass, with a maximum diameter of 10 cm; when sliced layer by layer, the cut surface was

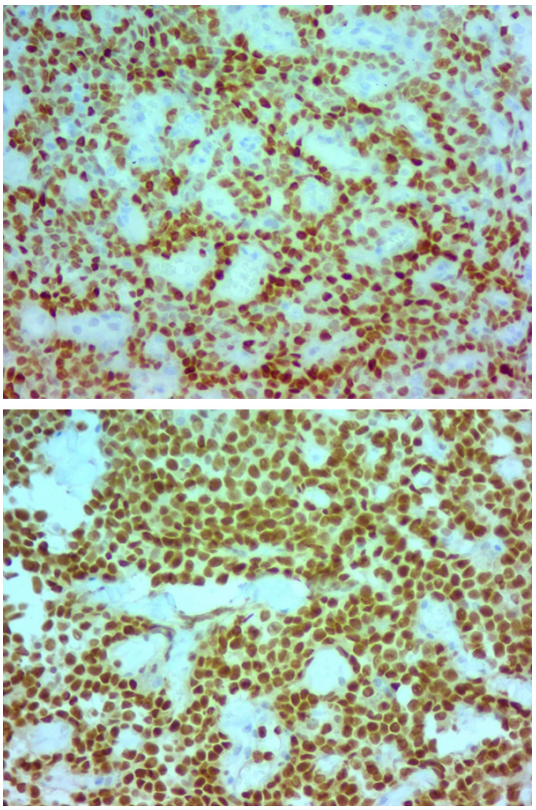

Figure 8. Diffuse positive expression of c-myc (IHC ×200).

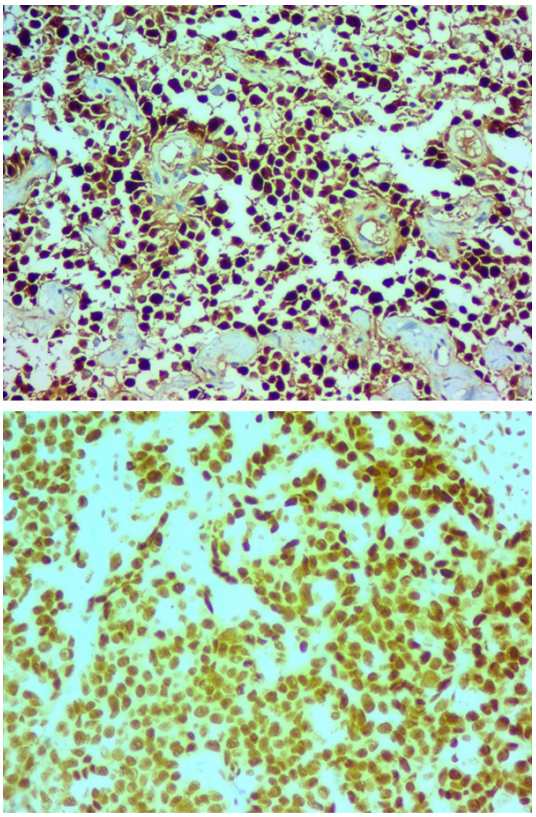

Figure 9. High index of Ki-67 in different areas (IHC ×200).

dark-red, microcystic and spongy hemorrhagic (**Figure 2**). The tumor is diffuse and infiltrating, without clear boundary.

Histologic features

All excisional biopsies, including skin and subcutaneous tissues, were examined with H&E staining. The histological pattern varied widely across tumors, as well as areas within the same tumor. The overlying epidermis was either hyperkeratotic and acanthotic or atrophic. Proliferation of reticular fibers was observed. In well or moderately differentiated areas, various sizes and forms of irregular lumens scattered in the dermis and subcutaneous tissue, partially communicating with each other, and shaping into channel-like structure. These channels were lined by one to several layers of moderately to severely atypical endothelial cells with hyperchromatic and pleomorphic nuclei, with occasional mitotic figures (**Figure 3**). This specific structure also dissected dermal collagen and obliterated appendages. On the contrary, in the undifferentiated areas, tumor cells were arranged in a solid pattern, consisting of large epithelioid cells with pleomorphic nuclei and prominent nucleoli. The endothelial cells were round or oval in shape, with prominent mitosis (**Figure 4**).

Immunohistochemical features

Staining for CD34, CD31 (**Figure 5**), D2-40 (**Figure 6**), vimentin, β-catenin and Factor VIII revealed focally or strongly positive intra-cytoplastic and/or membrane immunoreaction in tumor cells. ERG (**Figure 7**), c-MYC (**Figure 8**) presented as focal or diffusely nucleus positive. Positivity of Ki-67wascounted as 30%-95% across 3 representative fields (**Figure 9**). Several cases presented negative reaction for D2-40. No positive staining was observed for CK, EMA, HMB-45, HHV-8, Melan-A and S-100. A summary of immunophenotype of tumor cells was presented in **Table 3**.

Discussion

Most of the 400 STS cases reported in the literature were women diagnosed in 5-15 years (average: 11 years) after radical mastectomy,

Table 3. Immunohistochemical characteristics of 17 STS

Case ID	CD31	CD34	D2-40	c-MYC	Ki-67 Index (%)	FVIII	β-catenin	ERG
1	++	-	++	N++	80	+	+	N+
2	++	-	++	N++	95	+	+	N++
3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4	++	++	++	N++	60	++	++	N++
5	++	++	+	N+	20	++	+	N++
6	++	++	-	N++	70	++	++	N++
7	++	-	++	N++	80	++	++	N+
8	++	++	+	N+	80	++	++	N++
9	++	-	-	N++	60	++	++	N++
10	++	++	-	N++	90	++	++	N++
11	++	++	++	N++	90	++	+	N+
12	++	++	++	N+	15	++	++	N++
13	++	++	++	N++	50	++	++	N++
14	++	++	-	N++	60	++	++	N++
15	++	++	++	N++	30	++	++	N+
16	++	++	++	N++	80	++	++	N++
17	++	+	++	N+	5	++	-	N++

+, focal positive staining; + +, diffuse positive staining; -, negative staining; N, nuclear staining.

with an incidence of 0.07%-0.45% [4]. The risk of STS would increase by 15.9% in patients receiving postoperative radiotherapy [5, 6]. Only a few cases occurred after surgery for cervical cancer [7], and a few originated from congenital chronic lymphedema [2]. Almost no racial difference in incidence and no association with AIDS or other immunodeficiency diseases were observed. The peak age of STS was between 65 and 70 years old, corresponding to trends in breast cancer age-of-onset with additional years for the development of chronic lymphedema [8]. Another study reported an average age of onset at 68.8 years with a range from 44 to 84 years [9]. Typical clinical manifestations evolve as the following: in the early stage, multiple red, blue macular or papular nodules scatter subcutaneously but not easily detectable, and then gradually turn to erythema. In the later stage, satellite foci, hemorrhagic masses and even gangrene, resulting from intermittent hemorrhage and infection, can develop.

In this small cohort, we divided the cases into two groups: malignancy vs. chronic congenital lymphedema. Overall, STS was more common in women particularly in the group of malignancy; the distinction in the latter group is still unclear on account of limited cases. The number of lesions located in the lower limbs was comparable to that in the upper limbs. Patients with chronic congenital lymphedema were relatively younger (mean: 42.8 years) and developed STS after a longer interval from the presence of lymphedema to diagnosis (mean 22.4 years) compared to those with malignancy (mean age of onset: 66.9 years; mean latency: 14.4 years). One case receiving no adjuvant therapy developed STS in 10 years after radical cervical cancer. The fact may indicate radiation therapy is not an essential pathogenesis for STS.

Congenital or acquired chronic lymphedema was considered as the most important cause of STS. Although STS mainly developed after radical mastectomy, it might arise from congenital or acquired lymphedema attributed to trauma, filariasis, idiopathic lymphoma, venous stasis, morbid obesity, leg ulcerations, and invasion of groin from cervical or penile cancer [9-15]. Nevertheless, cardiogenic edema or renal disease caused edema is not associated with STS. Although it is widely accepted that lymphedema may induce angiosarcoma, the mechanism is yet to be illustrated. Local immunodeficiency resulted from long-standing chronic lymphedema may be involved in oncogenesis of STS. The affected area was immunocompromised as illustrated by Marek Stanczyk et al [16]. Lymphatic vessels on the edge of a tumor

formed an irregular network of bifurcated channels and variably sized lumens. Multiple lymphatic spaces and short, blind ending lymphatic vessels were located in the center, adjacent to the tumor.

Another hypothesisis is that long-term chronic lymphedema leads to local immune deficiency, and affected limb tissueaccumulatestissue fluid rich in proteins and growth factors. These growth factors may stimulate the formation of lymphatic vessels, collateral blood vessels, and finally, malignant tumors [17]. Recent studies have shown that overexpression of c-MYC, which is key for angiogenesis, is associated with secondary angiosarcoma (AS), including STS. One research applied fluorescence in situ hybridization (FISH) to analyze amplification of c-MYC in 28 primary and 33 secondary angiosarcomas (31 cases secondary to irradiation, 2 cases secondary to chronic lymphedema). A high level of c-MYC amplification located on chromosome 8q24. 21 was observed as a recurrent genetic alteration exclusively in 55% of AS secondary to irradiation or chronic lymphedema. Amplification of c-MYC was not predisposed to high-grade morphology [18]. Another study analyzed c-MYC amplification by FISH and expression by immunohistochemistry to investigate its diagnostic utility for discriminating angiosarcoma from atypical vascular lesion (AVL). All cases (7 with post-radiation AS and 1 with lymphedema-associated AS) demonstrated a high level of c-MYC amplification. In contrast, all AVLs were negative for c-MYC amplification. Additionally, all AS cases demonstrated nuclear positivity for c-MYC, whereas all AVLs were negative [19]. Consistently, in our cohort, c-MYC was overexpressed in all 17 cases of STS regardless of etiology. Thus, MYC amplification illustrated by FISH or overexpression by immunohistochemistry might be used to support the diagnosis of STS.

Meanwhile, positive and stable expression of CD31 and ERG presented in all cases. ERG, as a member of ETS family transcription factors, is expressed in vascular endothelial cells and regulates angiogenesis and apoptosis of endothelial cells. It is a highly sensitive and specific marker of vascular endothelial differentiation.

The differential diagnosis for STS includes both benign and malignant vascular diseases. Among the lymphatic neoplasms, benign lymphangioendothelioma (BL) represents a very rare but most confusing scenario, characterized by lymphatic vascular proliferation, histopathologically mimicking cutaneous low-grade angiosarcoma. However, very subtle distinctions exist, such as few lesions involving superficial dermis and extending into subcutaneous fat. In spite of significant proliferation of irregular or anastomosing vascular structures, the lining epithelial cells present moderately atypia with mildly hyperchromatic and pleomorphic nuclei, without apparent mitotic figures. As to prognosis, BL has a favorable outcome, without local invasion or metastases after excision [20].

Kaposi sarcoma (KS) is extremely difficult to distinguish from STS. Lymphedema is not essential but a relatively important induced factor for the development of KS. Hence, to differentiate STS from KS with lymphedema can be challenging, both clinically and histologically. In contrast to STS, KS is positive for human herpesvirus 8 (HHV-8) and less commonly associated with lymphedema [2].

Due to the rarity of STS, there is no standardized therapy for this disease. Radical surgery by local resection with a negative margin is the most widely applied treatment [21-23], and complete tumor resection predicts improved prognosis. However, local excision is always followed by recurrence. Therefore, once the biopsy specimen has been diagnosed as STS, extensive resection, early amputation or dissection of the joint and diseased limb are highly recommended, which may increase the survival rate of patients. The efficacy of amputation is superior to locally enlarged resection. Local recurrence rate is still very high even if the margin of primary surgery expands to 2-3 cm away from the lesion [7]. Grobmyer et al [24] reported no difference in survival rates between postoperative chemotherapy and radiotherapy. The incidence of recurrence or metastasis remains high after surgery even with radiotherapy and chemotherapy. Immunotherapy can be used as a palliative treatment for metastatic cases with pleural effusion [17, 25]. There is another hypothesis that blocking lymphatic and angiogenic pathways may inhibit tumor growth and metastasis [25, 26], which needs to be further studied.

Collectively, STS has poor prognosis and is prone to local recurrence and distant metastasis. Once the disease is diagnosed, the median survival time is about 2.5 years, and most patients develop metastatic diseases and die within 2 years [7, 25, 26]. The survival time of untreated patients is only 5-8 months. In this group, only 2 patients were treated with amputation or disarticulation, and the rest with extended resection. All patients were treated with postoperative radiotherapy, with survival time ranged from 3 to 30 months. Therefore, a better understanding of STS is required to improve clinical outcome. Regularly follow-up for the high-risk patients with radical mastectomy, radical resection for cervical cancer, and long-term chronic lymphedema is critical to prevent delay of diagnosis. In fact, substantial interval may exist between the first notice of the lesion and the final diagnosis of STS, which requires biopsy/specimen for histologic examination. Thus, timely biopsy of a suspicious lesion is an effective method to achieve the purpose of early diagnosis and early treatment. With regard to the excised specimen, we propose comprehensive immunohistochemical analysis of c-MYC and ERG, which can assist in making a timely correct diagnosis of STS.

Disclosure of conflict of interest

None.

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