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Original Article

A clinicopathologic study of 13 cases of primary lymphoma in soft tissue and review of literature

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Abstract: Primary lymphoma in soft tissue is very rare. In order to understand the clinicopathological features of primary lymphoma in soft tissue, we found 13 cases (0.3%) of primary lymphoma in soft tissue by reviewing 4303 lymphomas diagnosed in our institution from 2010 to 2019. Tumors were found in the following sites: 8 in lower extremity (2 in leg, 1 in calf, 1 in knee and 4 in buttock), 1 in upper extremity (left shoulder) and 4 in the trunk (3 in waist and 1 in thoracolumbar). The most common histologic type was DLBCL (7/13, 54.8%). 6 cases of which had follow-up information. 25 patients were also selected by screening the English literature search (from Jan 2010 to December 2019) including 1102 studies. Compared to the results of literature review, our results are similar with them. The tumor sites were as follows: 10 in lower extremity, 4 in upper extremity, 9 in the trunk and 2 in masticatory muscle. The most common histological type was also DLBCL (n=11/25, 44%). Overall survival analysis of all 31 patients including our 6 cases with primary lymphoma in soft tissue showed no significant difference between different histological type (Log Rank P=0.120, Breslow P=0.157). The differential diagnosis includes malignant melanoma, rhabdomyosarcoma and metastatic carcinoma in soft tissue.

Keywords: Soft tissue, lymphoma, clinicopathologic feature, immunohistochemistry, differential diagnosis

Introduction

Non-Hodgkin lymphomas (NHL) usually present in lymphoid organ or extranodal site containing lymphoid tissue and the bone marrow. Primary lymphomas in soft tissue is extremely rare estimated to occur in 0.1% of all lymphomas [1] and 0.01% of all soft tissue tumor [2]. Some soft tissue lymphomas are related with HIV infection [3, 4] or Rheumatoid Arthritis [5]. Patients usually have symptoms like a soft tissue mass, swelling, and pain. The literature indicate that the most common histology is diffuse large B cell lymphoma (DLBCL), but almost all types of NHL have been described [6-10]. The main sites commonly involved are lower extremity, particularly thigh and calf [11-14]. Peculiar imaging characteristics might help to differentiate soft tissue lymphomas from soft tissue sarcomas by using magnetic resonance imaging (MRI) or computed telegraph (CT) [15, 16]. Treatment of non-Hodgkin lymphoma is based on the histologic type, clinic stage, immunophenotype, and symptoms [17]. So far, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is the standard chemotherapy scheme for DLBCL, the cure rates of which is exceeding 50% [18], while Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) is preferred for ALCL [17]. In former study, we had described clinicopathologic features of lymphoma in soft tissue from 1999 to 2010 [6]. In this report, we continued to study primary lymphoma in soft tissue diagnosed in our institution from 2010-2019, we found 13 cases (0.3%) by reviewing 4303 lymphomas, summarized the clinicopathologic features and put forward differential diagnosis. Moreover, we systematically reviewed the available data from the English literature in the past 10 years.

Materials and methods

Clinical assessment

The definition of soft tissue is that it could support and connect the surrounding structures such as connective tissue, adipose tissue and skeletal muscle, excluding bone [1]. The gener-

ally acknowledged criteria for primary lymphoma in soft tissue were originally described by Lanham et al. [19] and were adopted by our former published article [6]. This research also use the same criteria. They are as follows: (1) the tumor occurs in the soft tissue (including adipose tissue, connective tissue, and skeletal muscle tissue); (2) the patient has no previous history of lymphoma; (3) lymphoma is not found in more than two locations including the lymph nodes or extranodal organs; (4) a mass is not found in the thoracic and abdominal cavities or visceral organs; (5) cases should be excluded if tumor occurs in sites with abundant lymphoid tissue, such as skin, bone, axilla, groin, scalp, face, and retroperitoneum; (6) lymph node structure should not be observed in the biopsy specimen. Thus, only 13 cases were selected from 4303 patients with lymphoma diagnosed in The First Affiliated Hospital, Sun Yat-sen University from Jan. 2010 to Dec. 2019 by reviewing the clinical and imaging data, including ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography (PET)-CT. Prior patient consent and approval from the Institutional Research Ethics Committee were obtained.

Immunohistochemical analysis and histopathologic examination

Tissues were fixed in 4% formaldehyde and embedded in paraffin. Four-micrometer-thick sections were cut from the tissue blocks and stained using routine HE staining. Immunohistochemistry staining was performed by using an EnVison Kit (Dako). The following primary antibodies purchased from Dako Corporation were used: CD20, CD79a, CD3, CD5, CD4, CD8, BCL6, BCL2, CD10, MUM1, CD99, Granzyme B, CD30, CyclinD1, MPO, S-100, HMB45, MelanA, anaplastic lymphoma kinase (ALK), cytokeratin, Vimentin, Myogenin, MyoD1, terminal deoxynucleotidyl transferase (TdT), TIA-1, C-myc and Ki-67. All histopathologic sections were reviewed by two experienced pathologists according to the World Health Organization (WHO) 2016 classification of tumors of lymphoma.

In situ hybridization

In addition to the IHC profiling, Epstein-Barr virus (EBV) infection was analyzed by in situ hybridization of EBV-encoded small RNAs (EBERs). It was carried out using a cocktail of fluorescein isothiocyanate-labeled oligonucleotides complementary to the nuclear EBERs, following the manufacturer's instructions (Dako), as previously described [20]. Positive EBERs in situ hybridization showed dark brown nuclei. An EBERs-positive nasopharyngeal carcinoma specimen was used as positive control. A 1 mol/L concentration of Tris-buffered saline was used as the negative control in each run.

Literature meta-analysis

A systematic search of the available literature from 2010 to 2019 was conducted in the PubMed and Cochrane database. Keywords used for the literature search were soft tissue and lymphoma. Because of the lack of published clinical trials on this issue, all studies describing patients affected by soft tissue lymphomas, with available information on clinic characteristics, treatment strategies, and follow-up information, were included in this analysis. There were 1046 records in Pubmed and 56 records in Cochrane, only 22 studies were included in quantitative synthesis excluding duplicates and unrelated records. The accuracy of this meta-analysis was assessed using the checklist of items in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (**Figure 1**).

Statistical analysis

The primary end points were overall survival (OS). OS was defined as the time from registration to the observation of death as a result of any cause. The results of the study were analyzed statistically using the SPSS 8.0 software program (SPSS Inc., Chicago, IL). Differences between groups were evaluated by using the log-rank test and OS curves were plotted by the Kaplan-Meier method. P value <0.05 was considered statistically significant.

Results

Clinical features

All 13 patients that mentioned above presenting with soft tissue mass and local swelling with or without pain were transferred to our hospital for final diagnosis and treatment. The clinicopathological analysis were as follows:

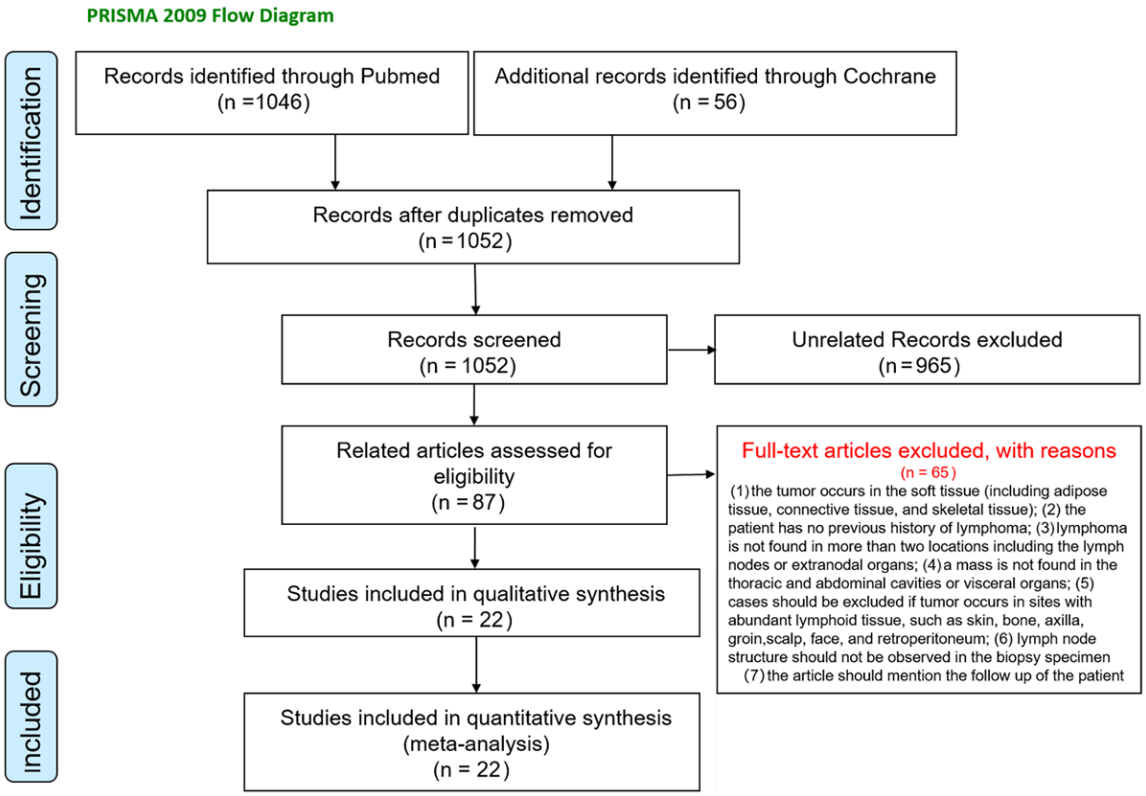

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

The male-female ratio was 11:2. The mean age was 46.2 years ranging from 7 to 79 years. There were 3 teenagers (0-17 years old), 2 young people (18-40 years old), 5 middle-aged (41-65 years old), and 3 old people (over 65 years old). The tumor sites were as follows: 8 in lower extremity (2 in leg, 1 in calf, 1 in knee and 4 in buttock), 1 in upper extremity (left shoulder) and 4 in the trunk (3 in waist and 1 in thoracolumbar). The most common site of tumors apparently was the lower extremity. The average diameter of tumor is 10 cm ranging from 2 to 17 cm. The most common histological type was DLBCL (n=7, 53.85%). Besides, there were 4 T cell lymphoma (3 anaplastic large cell lymphoma, ALCL; 1 peripheral T cell lymphoma, NOS) and 2 high grade B cell lymphoma. Follow-up data was available for 6 of the patients. 1 patient underwent chest and back tumor resection in the other hospital two year ago, but died 33 months after diagnosis. 1 received chemotherapy (Dumex + Osenda), but died 39 months after diagnosis. 2 patients were still under therapy in which that one received Dexamethasone (d1-d5) + Cyclophosphamide (d4-5) + AA + MTX and the other received Hexan + Pirarubicin + Vincristine. The last 2 patients were alive without evidence of recurrence in which that one received Pirarubicin + vincristine and the other received CHOP. The clinicopathological features of 13 cases of primary soft tissue lymphoma were shown in **Table 1**.

Histopathologic findings, immunohistochemistry staining, and in situ hybridization

According to the WHO (2016) classification of tumors of lymphoma, 13 cases of primary lymphoma in soft tissue were included. Histological types were as follows.

B-cell lymphoma (n=9): In the 9 cases of B cell lymphoma, 7 cases were DLBCL. Histologically, the tumor was composed of medium-large sized round or oval tumor cells with oval to irregular nuclei, vesicular chromatin, and high mitotic activity. A few small lymphocytes and plasma cells were scattered within the tumor. Tumor cells infiltrated the skeletal muscle or adipose tissue (**Figure 2A**, **2B**). Tumor cells

Table 1. Clinicopathologic features of 13 cases of primary lymphoma in soft tissue

Case no.	Sex/ age	Symptoms	Localization	Tumor size (cm)	Subtype of lymphoma	EBERs	Treatment	Follow-up
1	M/73	Right calf swelling for more than 3 months	Right calf	7.5×6×10	DLBCL, GC	ND	NA	NA
2	M/79	Pain in left hip with numbness in left lower limb for 4 months	Left hip	12×11.4×12.5	DLBCL, GC	(-)	R-CHOP	NA
3	M/45	NA	Right back waist	NA	DLBCL, GC	ND	NA	NA
4	M/11	Malignant tumor in the left gluteal muscle	Left hip	4.5×3×7.5	DLBCL, GC	ND	Exision + chemotherapy	NA
5	F/73	NA	Left shoulder	NA	DLBCL, GC	ND	NA	NA
6	M/35	Soft tissue mass in the left thigh	The back of left thigh	11.1×5.2×17.4	DLBCL, non-GC	(-)	Pirarubicin + vincristine	No evidence of disease 31 months
7	M/51	Back pain with right thigh numbness in February, worsening for 2 weeks	Thoracolumbar	7×8	DLBCL, non-GC	ND	Chest and back resection in the outer hospital 1 year ago	Died 33 months after diagnosis
8	F/64	Pain in the right waist with numbness in the proximal part of the right thigh for 2 months,worthning for 10 days	Right back waist	3.5×3.6×3.8	Invasive B cell lymphoma, between Burkitt and DLBCL (high grade B cell lymphoma)	ND	NA	NA
9	M/7	A mass in the right waist gradually grow bigger, with numbness in the right lower limb for more than 3 months	Right back waist	17×6.1×7.2	high grade B cell lymphoma	(-)	DEX (d1-d5) + CTX (d4-5), Mellow, AA, MTX	Still under theropy
10	M/63	50 days after right hip replacement, right hip pain for 2 weeks	Right hip	9.4×4.2	ALK (-) ALCL	(-)	CHOP	NA
11	M/23	Malignant neoplasm of the lower quadriceps in the right thigh	Right thigh	4.1×2.2×6	ALK (+) ALCL	(-)	Hexan + Pirarubicin + Vincristine	Still under theropy
12	M/13	Left hip swelling and pain for more than 3 months	Tail of sacrum	7×3	ALK (+) ALCL	(-)	CHOP	No evidence of disease 33 months
13	M/63	Right knee pain for 1 year	Lower right knee	9.7×6.8×15.7	PTCL	(+/-)	Dumex + Osenda	Died 39 months after diagnosis

AA, Aclacinomycin + Cytarabine; ALCL, anaplastic large cell lymphoma; CTX, Cyclophosphamide; DEX, Dexamethasone; DLBCL, diffuse large B-cell lymphoma; EBER, Epstein-Barr virus-encoded small non-polyadenylated RNA; GC, germinal center; MTX, methotrexate; ND, not done; NA, not available; PTCL, peripheral T cell lymphoma; R-CHOP, rituximab to cyclophosphamide, doxorubicin, vincristine, and predisone.

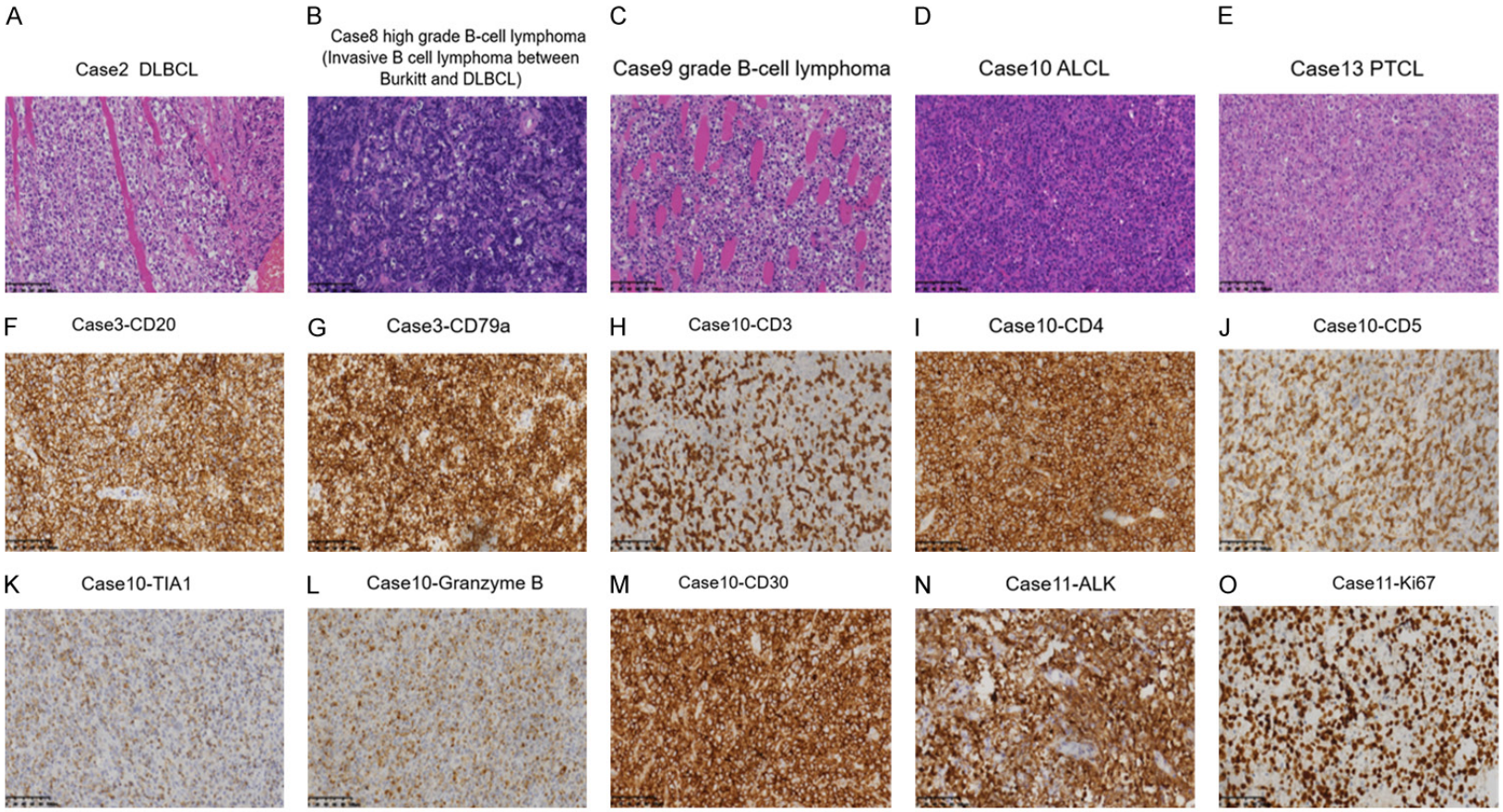

Figure 2. HE and immunohistochemistry staining of different types of primary lymphoma in soft tissue. A. DLBCL infiltrated skeletal muscle; B. The diffusely infiltrated small oval blue tumor cells in high grade B-cell lymphoma (Invasive B cell lymphoma between Burkitt lymphoma and DLBCL); C. High grade B-cell lymphoma infiltrated skeletal muscle; D. ALCL tumor cells diffusely distributed and had classical nuclear morphology; E. PTCL tumor cells diffusely distributed. HE ×200; F, G. DLBCL was positive for CD20 and CD79a; H-N. ALCL was positive for CD3, CD4, CD5, TIA-1, Granzyme B, CD30, and ALK; O. Ki-67 index was high. IHC ×200.

were diffuse and strongly positive for CD20 and CD79a (**Figure 2F**, **2G**). In some cases, BCL6, BCL2, CD10, MUM1 were positive, the positive status of CD10, BCL6, and MUM1 could be used to determine whether DLBCL is originate from germinal center. Therefore, two cases were non-germinal center phenotype and five were germinal center phenotype using a panel of CD10, BCL6, and MUM-1 immunostaining. The positive rate of Ki-67 expression was approximately 50%-95%. All seven DLBCLs were negative for EBERs by in situ hybridization (**Table 2**).

In addition, two cases were high grade B cell lymphoma, one was taken from the lower back. The tumor tissue infiltrated striated muscle and fibrous tissue under the microscope. Some tumor cells were large with rich cytoplasm and some of tumor cells were medium-large, deeply stained (**Figure 2C**). CD20, CD79a, CD10, BCL6 were positive. Vimentin was partly positive. Ki-67 was positive in about 80% tumor cells. Tumor cells showed that there was no C-myc, and IGH or BCL2 and IGH gene fusion by FISH. This case was finally diagnosed as high grade B cell lymphoma (invasive B cell lymphoma, between Burkitt lymphoma and DLBCL). The other case was also taken from the lower back. The nucleus was medium-sized and deeply stained, CD20, CD79a, BCL6 and CD99 were positive. BCL2 was partly positive. Ki-67 was positive in about 90% tumor cells. CD3, CD5, Myogenin, MyoD1, CK, S-100, TdT, CD10, MPO, and EBER were negative. FISH detection showed no C-myc or BCL6 gene breakage or fusion of BCL2 and IGH. This case was finally diagnosed as high grade B cell lymphoma.

For this histological type, 3 patients had follow-up information, one patient with high grade B cell lymphoma underwent chest and back resection in the other Hospital 2 year ago, but died 33 months after diagnosis. One patient with Invasive B cell lymphoma between high grade B cell lymphoma and DLBCL was still under therapy, receiving Dexamethasone (d1-d5) + Cyclophosphamide (d4-5) + AA + MTX, the last patient with DLBCL were still alive without evidence of recurrence and received pirarubicin + vincristine.

Anaplastic large cell lymphoma, ALK-positive (n=3): The tumor consisted of large lymphoid cells with abundant cytoplasm and pleomorphic nuclei. Some tumor cells manifested horseshoe- or doughnut-shaped nuclei or were multinucleated (**Figure 2D**). The tumor cells were positive for CD3, CD4, CD5, TIA-1, Granzyme B, CD30, and ALK, but negative for HMB45, S-100, Melan A, MyoD1, Myogenin. Ki-67 staining showed high proliferation of the tumor (**Figure 2H-O**). Two patients had follow-up information, one was still alive without evidence of recurrence and received CHOP. The other patient with ALK (+) ALCL received Hexan + Pirarubicin + Vincristine chemotherapy.

Peripheral T cell lymphoma, not otherwise specified (n=1): The tumor consisted of numerous small and medium-sized cells with irregular, pleomorphic, hyperchromatic, or vesicular nuclei and clear cytoplasm. A complicated inflammatory background including small lymphocytes, eosinophils, plasma cells, and clusters of epithelioid histocytes was observed (**Figure 2E**). Tumor cells were positive for T cell marker including CD4, CD8, and CD99. Vimentin was also positive, but negative for CD20, CD79a, CD10, TdT, CD30, ALK, and TIA-1. EBER was negative. Based on the follow-up information, one patient with PTCL received chemotherapy (Dumex + Osenda), but died 39 months after diagnosis.

Literature meta-analysis

We screened the English literature search (from Jan 2010 to December 2019) including 1102 studies. Of these, 1080 studies were excluded because of duplicates, not related, missing or incomplete data regarding histology, clinic characteristics, treatment, and follow-up information. Finally, 22 studies [4, 5, 9, 10, 21-37] including a total of 25 patients were included. The clinicopathological features of all 25 patients plus our 6 cases with follow-up information were finally analyzed synthentically. The data was shown in **Table 3**. The clinicopathological analysis of 25 patients were as follows: The male-female ratio was 12:13. The mean age was 56.4 years ranging from 14 to 89 years. The number of adults was significantly more than young people, 20 of them were over 40 years. The average diameter of tumor is 9 cm ranging from 4 to 20 cm. The tumor sites were as follows: 10 in lower extremity, 4 in upper extremity, 9 in the trunk and 2 in masticatory muscle. The most common site of

Table 2. The expression of immunohistochemistry markers in 13 cases of primary lymphoma in soft tissue

Case	histotype	CD20	CD79A	CD3	CD5	CD4	CD8	BCL6	BCL2	CD10	MUM1	TDT	CD99	TIA	GranzymeB
1	DLBCL, GCB	(+)	(+)	(-)	(-)	0	0	(+)	(+)	(-)	(-)	0	0	0	0
2	DLBCL, GCB	(+)	(+)	(-)	(-)	0	0	(+)	(+)	(-)	(-)	(-)	0	0	0
3	DLBCL, GCB	(+)	(+)	(-)	(-)	0	0	(+)	(-)	(-)	(-)	0	0	0	0
4	DLBCL, GCB	(+)	(+)	(-)	(-)	0	0	(+)	(+)	(-)	0	(-)	0	0	0
5	DLBCL, GCB	0	(+)	(-)	(-)	(-)	0	(+)	0	(+)	(+)	(-)	0	0	0
6	DLBCL, non-GCB	(+)	(+)	(-)	(-)	0	0	(+)	(+)	(+)	(+)	0	0	0	0
7	DLBCL, non-GCB	(+)	(+)	(-)	(-)	0	0	(+)	(+)	(-)	(+)	0	0	0	0
8	High grade B cell lymphoma (Invasive B cell lymphoma, between Burkitt and DLBCL)	(+)	(+)	(-)	0	0	0	(+)	(+/-)	(+)	(-)	0	(-)	0	0
9	High grade B cell lymphoma	(+)	(+)	(-)	(-)	0	0	(+)	(+)	(-)	0	(-)	(+)	0	0
10	ALK (-) ALCL	(-)	0	(+)	(-)	(+)	(-)	(-)	0	(-)	(+)	0	0	(+)	(+)
11	ALK (+) ALCL	(-)	(-)	(+)	(-)	0	(-)	(+)	0	(-)	(+)	(-)	0	(+)	0
12	ALK (+) ALCL	(-)	(-)	(+)	(+)	(+)	0	0	0	0	0	0	0	(+)	(+)
13	Peripheral T cell lymphoma	(-)	(-)	(+)	(-)	(+)	(+)	0	(+)	0	0	0	(+)	0	0

Case	histotype	CD30	ALK	CMYC	Vimentin	CK	CyclinD1	MPO	Myogenin	MoyD1	S-100	HMB45	MelanA	KI67	EBER
1	DLBCL, GCB	0	0	0	(+)	(-)	0	0	0	0	(-)	(-)	(-)	50%	0
2	DLBCL, GCB	(-)	0	0	0	(-)	0	(-)	0	0	0	0	0	80%	(-)
3	DLBCL, GCB	0	0	0	0	(-)	(-)	0	0	0	0	0	0	80%	0
4	DLBCL, GCB	0	0	(+/-)	0	(-)	(+)	0	0	0	0	0	0	80%	0
5	DLBCL, GCB	(-)	(-)	0	(+)	(-)	(-)	(-)	0	0	(-)	0	0	95%	0
6	DLBCL, non-GCB	(+)	(-)	(+)	0	0	(-)	0	0	0	0	0	0	95%	(-)
7	DLBCL, non-GCB	0	0	(-)	0	(-)	(-)	0	0	0	0	0	0	50%	0
8	High grade B cell lymphoma (Invasive B cell lymphoma, between Burkitt and DLBCL)	(-)	(-)	0	(+)	(-)	0	0	0	0	0	0	0	80%	0
9	High grade B cell lymphoma	0	0	0	0	(-)	(-)	(-)	(-)	(-)	(-)	0	0	90%	(-)
10	ALK (-) ALCL	(+)	(-)	0	0	0	0	0	0	0	0	0	0	85%	(-)
11	ALK (+) ALCL	(+)	(+)	0	0	(-)	0	(-)	(-)	(-)	0	0	0	80%	(-)
12	ALK (+) ALCL	(+)	(+)	0	(+)	(+)	0	0	0	0	(-)	(-)	(-)	80%	(-)
13	Peripheral T cell lymphoma	0	0	0	(+)	(-)	0	0	(-)	(-)	0	0	0	70%	(+/-)

Table 3. The clinicopathologic features of 31 soft tissue lymphoma cases (25 cases from literature and 6 cases from our institution)

Case	Age	Sex (male 1, female 2)	Medical history	average Size (cm)	Localization	Histologic type	Dead or not (yes 1, no 0)	Follow-up informtion (month)
1	49	1	a 3-month history of progressive asymmetry of the face	6	masseter muscle	DLBCL	0	72
2	76	2	“lumps” in her right temple and neck	6	widespread skeletal muscle, masticatory muscle, and parotid gland	high-grade DLBCL	0	10
3	77	2	with a 20-year history of seropositive RA involving both hands presented to her primary care provider	5.5	left hand	DLBCL	0	66

4	86	2	continuous, progressive and high intensity pain that was more frequent at night and localized in the right dominant hand	20	forearm muscle	DLBCL	0	6
5	40	1	swelling of the right side of the labia and oral mucosa	NA	neck extensor muscles	PTCL-U	0	6
6	51	2	a 2-month history of severe pain and swelling of the right leg	NA	skeletal muscles from the gluteus to femoris	ALK-negative ALCL	1	2
7	89	1	a three-month history of swelling of his left thigh and slight fever	6.5	thigh muscle	ALK-negative ALCL	1	1
8	45	2	a one-year and eight-month history of tenderness in her right thigh	NA	right thigh and left iliacus muscle	DLBCL	0	36
9	14	2	a 2-month history of left leg pain	8	left psoas muscle	ALK-positive ALCL	0	50
10	81	1	a 3-month history of severe pain and slight thickness in the left thoracic paravertebral region	4	the left thoracic paravertebral region	B-Cell Lymphoma, Unclassifiable	1	1
11	35	1	HIV RELATED	NA	chest wall and upper leg	plasmablastic lymphoma	1	1
12	46	1	HIV RELATED	NA	chest wall	DLBCL	0	6
13	37	1	HIV RELATED	NA	chest wall and scalp	plasmablastic lymphoma	1	1
14	48	1	HIV RELATED	NA	chest wall	BL	1	12
15	63	1	a 10-day history of pain on the left side of the chest that was described as burning and spreading to the right side	NA	in the soft tissues of the breast, right gluteal region and left leg	plasmablastic lymphoma.	0	8
16	33	1	one month history of a painful red nodule over his left chest wall	20	chest wall	BL	1	1
17	62	2	a one-month history of painful left lower leg swelling and paresthesia of the medial side of the foot after falling over	NA	left leg	between diffuse large B-cell lymphoma and Burkitt lymphoma	1	1
18	72	1	neck pain of three-day duration, described as radiating to the upper back and shoulders	7	triceps muscle	DLBCL	0	5
19	75	2	a painless, slowly growing mass on the dorsum of the right wrist	7	right wrist	DLBCL	1	11
20	52	2	with a 3-week history of left gluteal pain	6	in the left gluteal muscle	DLBCL	0	8
21	41	2	a painful mass in the right lower extremity that was impeding walking	12	the right femur	DLBCL	0	6
22	71	2	swelling with pain, skin redness, and increasing skin temperature in the right hip	NA	the right hip	non Hodgkin marginal zone B cell lymphomas	0	3
23	68	2	a 2-month history of a mass in the poste rior part of the right thigh and a 1-month history of movement disorder of the right lower leg	16	the right thigh	DLBCL	1	6
24	24	1	one-month history of left lower back pain, which had been exacerbated for 10 days prior to admission	11	in the left psoas	ALK-nagative ALCL	0	6
25	76	2	a 1-year history of right foot numbness, which gradually worsened	5	right thigh and calf	DLBCL	1	16
26	35	1	Soft tissue mass in the left thigh	11	the back of left thigh	DLBCL, non-GCB	0	31
27	51	1	Back pain with right thigh numbness in February, worsening for 2 weeks	7.5	thoracolumbar	DLBCL, non-GCB	1	33
28	7	1	A mass in the right waist gradually grow bigger, with numbness in the right lower limb for more than 3 months	10	right back waist	high grade B cell lymphoma	0	8
29	23	1	Malignant neoplasm of the lower quadriceps in the right thigh	4	right thigh	ALK (+) ALCL	0	21
30	13	1	Left hip swelling and pain for more than 3 months	5	Tail of sacrum	ALK (+) ALCL	0	33
31	63	1	Right knee pain for 1 year	11	lower right knee	PTCL	1	39

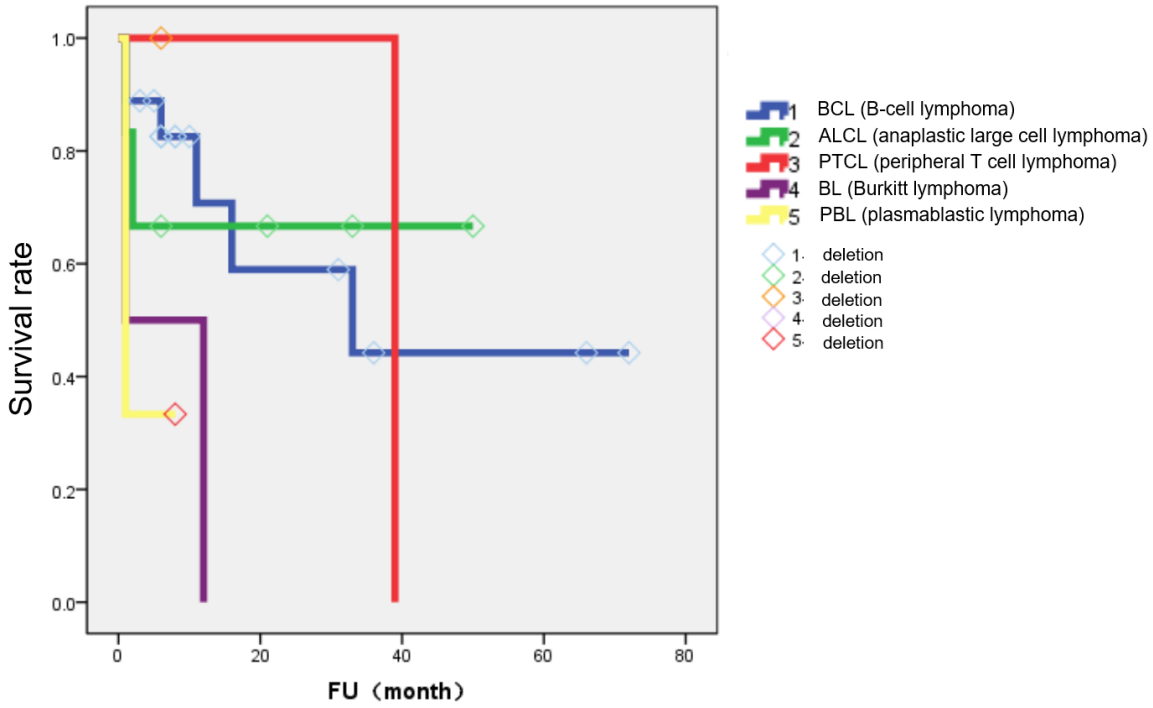

Figure 3. Overall survival analysis of 31 primary lymphomas in soft tissues. 1 BCL (B-cell lymphoma); 2 ALCL (anaplastic large cell lymphoma); 3 PTCL (peripheral T cell lymphoma); 4 BL (Burkitt lymphoma); 5 PBL (plasmablastic lymphoma); Log Rank P=0.120, Breslow P=0.157.

tumors apparently was the lower extremity followed by the trunk. The most common histological type was DLBCL (n=11, 44%). Besides, there were 5 T cell lymphoma (4 anaplastic large cell lymphoma, ALCL; 1 peripheral T cell lymphoma, NOS), 3 plasmablastic lymphoma, 2 high grade B cell lymphoma, 2 BL (Burkitt lymphoma), 1 marginal zone B cell lymphomas and 1 B-Cell Lymphoma, Unclassifiable. All 25 patients had follow-up data. Overall survival analysis of all 31 patients including our 6 cases with primary lymphoma in soft tissue showed no significant difference between different histological type (**Figure 3**, Log Rank P=0.120, Breslow P=0.157).

Discussion

Primary lymphoma in soft tissue is rare. We found 13 patients with primary lymphoma arising from soft tissue in 4303 lymphoma cases diagnosed in our institution by using strict criteria. We selected 25 patients by screening the English literature search (from Jan. 2010 to December 2019) including 1102 studies. Compared to the results of literature review, our results are similar. Both of the results showed that the tumor were more common in middle-aged and elderly people, the most common sites were lower extremities and the leading histological type is DLBCL. It is also consistent with Salamao's results [38] and other studies [6, 38, 39]. Besides, almost all types of NHL have been found in soft tissue [6-10]. For pathology diagnosis, we need to differentiate primary DLBCL in soft tissue from other tumors by morphological changes, immunophenotype and molecular profile. Primary lymphoma in soft tissue could mimic metastatic carcinoma, malignant melanoma, rhabdomyosarcoma, and other sarcomas [13]. A panel of primary antibodies and/or molecular technique should be used. CD20, CD79a, CD10, BCL6 and MUM1 could be positive for DLBCL. CD10, BCL6 and MUM1 could help distinguish from GCB type and non GCB type. BCL2 and/or BCL6 rearrangement in combination with MYC rearrangement could help diagnose high grade B cell lymphoma. Some study have even found a lot of immunoglobulin inclusions in B cell lymphoma [11]. However, metastatic carcinoma commonly arrange in nest and are positive for epithelial markers. Malignant melanoma is composed of large tumor cells with remarkable

nucleoli, which is similar to DLBCL, but the tumor cells of malignant melanoma are positive for HMB45, Melan-A and S-100 protein. Rhabdomyosarcoma is common in soft tissue and most of tumor cells are spindle or epitheleoid with prominent nucleoli. The tumor cells are positive for Desmin, MyoD1 and Myogenin. As for other sarcoma or tumors in soft tissue could be similar to DLBCL by morphology, it is important to find important clues and evidence. The ALCL could be positive for CD3, CD4, CD5, TIA, GranzymeB, CD30, and ALK, but negative for HMB45, S-100, Melan A, MyoD1 and Myogenin, which could exclude malignant melanoma and rhabdomyosarcoma.

Treatment of non-Hodgkin lymphoma is based on the histological type, clinic stage, and symptoms [17]. The current standard therapy for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), cure rates of which exceeding 50% [18], while Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) is preferred for ALCL [17].

We summarized 25 patients with primary lymphoma in soft tissue in the English literature, and combined with 6 patients who had follow-up information in our series, 31 patients were finally considered in the combined analysis. The OS analysis of all patients with primary lymphoma in soft tissue showed no significant different between different histological type. However, Derenzini et al. observed an inferior outcome for DLBCL compared with indolent B-cell NHL in soft tissue (5-year progression free survival: 34% vs. 64% in the combined analysis, respectively. P=0.01). Furthermore, the prognosis in the DLBCL group appears to be worse compared with the historical data of DLBCL patients treated with chemoimmunotherapy [1]. In our study, only 31 samples have follow-up data plus our 6 cases. Overall survival analysis of them shows no significant difference between different histological types. In my opinion, the shortcoming of the current study is that the number of cases meet the standard is too few. In the future, we hope to collect more samples for further research.

Disclosure of conflict of interest

None.

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