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【 CASE REPORT 】

Primary Skeletal Muscle Peripheral T-cell Lymphoma: An Autopsy Case Report and Review of the Literature

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Abstract:
Primary skeletal muscle lymphoma is extremely uncommon, and there have only been eight previous case reports on primary skeletal muscle peripheral T-cell lymphoma, not otherwise specified (PSM-PTCL, NOS). We herein report an autopsy case of a 71-year-old woman with PSM-PTCL, NOS, who had a 24-year history of systemic sclerosis treated with immunosuppressive drugs. A post-mortem examination revealed infiltration of lymphoma cells positive for T-cell markers, cytotoxic markers, and p53. This case was considered to be one of other iatrogenic immunodeficiency-associated lymphoproliferative disorder (OIIA-LPD). This is the first case categorized under both PSM-PTCL, NOS, and OIIA-LPD.

Key words: primary skeletal muscle lymphoma, peripheral T-cell lymphoma, not otherwise specified, other iatrogenic immunodeficiency-associated lymphoproliferative disorders, systemic sclerosis, autopsy

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Introduction

Primary extranodal lymphoma is known to occur in the gastrointestinal tract, skin, lungs, and central nervous system; however, primary skeletal muscle lymphoma (PSML) is extremely rare (1). B-cell lymphoma, represented by diffuse large B-cell lymphoma (DLBCL), is the most frequent entity in PSML.

Primary skeletal muscle peripheral T-cell lymphoma, not otherwise specified (PSM-PTCL, NOS), are a group of rare and aggressive lymphomas, with only eight previous reports on the condition published (2-9). Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) is the most common subtype of mature aggressive T-cell lymphoma, manifesting most often as a nodal disease (10).

We herein report a rare autopsy case of PSM-PTCL, NOS. In addition, our case was categorized as other iatrogenic immunodeficiency-associated lymphoproliferative disorder (OIIA-LPD). According to the World Health Organization's (WHO) 2017 classification, OIIA-LPD is defined as lymphoid proliferations or lymphoma that develops in patients receiving immunosuppressive drugs for autoimmune diseases (11). OIIA-LPD is mainly a B-cell lymphoproliferative disorder (B-LPD) or Hodgkin lymphoma (HL) type, whereas T-cell LPD (T-LPD) is relatively rare. Thus, there have been no previous reports on PSM-PTCL, NOS in OIIA-LPD. Our case differed from the eight previously reported PSM-PTCL, NOS cases with regard to the patient characteristics and clinical course. We believe that our clinicopathological findings provide additional information supporting our understanding of this rare lymphoma.

Case Report

The patient was 71-year-old woman. She had a history of surgery (osteosynthesis) for peritrochanteric femur fractures at 68 years old. She also had a 24-year history of systemic sclerosis (SSc), which was controlled with prednisolone (PSL) (5 mg/day) and cyclosporine (CyA) (100 mg/day). At 55 years old, she was diagnosed with pulmonary arterial hypertension (PAH) based on the results of right heart catheterization and started on beraprost and home oxygen therapy at another hospital. At 62 years old, she was transferred to

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our hospital because she had moved houses. Combination therapy with PSL and CyA was continued throughout the treatment period, and she received long-term administration.

Table 1. Laboratory Findings on Admission.

WBC	4,700 /μL	TP	5.2 g/dL
Neutrophil	78 %	Alb	3.1 g/dL
Lymphocytes	9 %	T-Bil	0.8 mg/dL
Monocytes	12 %	AST	74 IU/L
RBC	298 $\times 10^4$/μL	ALT	18 IU/L
Hb	10.1 g/dL	LDH	2,129 IU/L
Hct	30.9 %	CPK	21 U/L
PLT	4.1 $\times 10^4$/μL	BUN	29.8 mg/dL
PT-INR	1.08	Cre	0.66 mg/dL
APTT/NC	33.0/26.8 s	UA	5.5 mg/dL
FIB	261 mg/dL	CRP	8.0 mg/dL
D-dimer	1.9 μg/dL	sIL-2R	6,313 U/mL
HIV	-	KL-6	233 U/mL
HTLV-1	-		

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, PLT: platelet, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, NC: normal control, FIB: fibrinogen, HIV: human immunodeficiency virus, HTLV-1: human T-cell leukemia virus type I, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, BUN: blood urea nitrogen, Cre: creatinine, UA: uric acid, CRP: C-reactive protein, sIL-2R: soluble interleukin-2 receptor, KL-6: Krebs von den Lungen-6

Her activities of daily living (ADL) gradually weakened because of chronic respiratory failure and steroid-induced myopathy.

About one month before hospitalization, the patient's left thigh became progressively swollen, and she was admitted with complaints of trouble walking due to the pain. Contrast computed tomography (CT) revealed a 10-cm heterogeneous mass involving the left iliopsoas muscle, and highly elevated levels of serum soluble interleukin-2 receptor (sIL-2R) (6,313 U/mL) and lactate dehydrogenase (LDH) (2,129 IU/L) were observed (Table 1). Based on these findings, we suspected malignant lymphoma.

On admission, she had a temperature of 99 °F, and her oxygen saturation of hemoglobin at rest with 3 L/min oxygen supplementation was 92%. Swelling and diffuse redness of the left inguinal region and thigh, with left inguinal lymph node (LN) swelling, were observed. Laboratory studies revealed anemia and thrombocytopenia (hemoglobin level, 10.1 g/dL; platelet count, 4.1×10^4/μL). Positron emission tomography (PET) imaging with [^{18}F] fluorodeoxyglucose (FDG) demonstrated increased an uptake of FDG within the entire left iliopsoas muscle (Fig. 1). The abnormal muscle was isointense on T1-weighted imaging and hyperintense on T2-weighted imaging, with a heterogeneous mass (Fig. 2). A bone marrow (BM) examination showed normal cellularity and no evidence of abnormal cells.

We requested a biopsy of the left iliopsoas muscle tumor from an orthopedic doctor; however, the request was re-

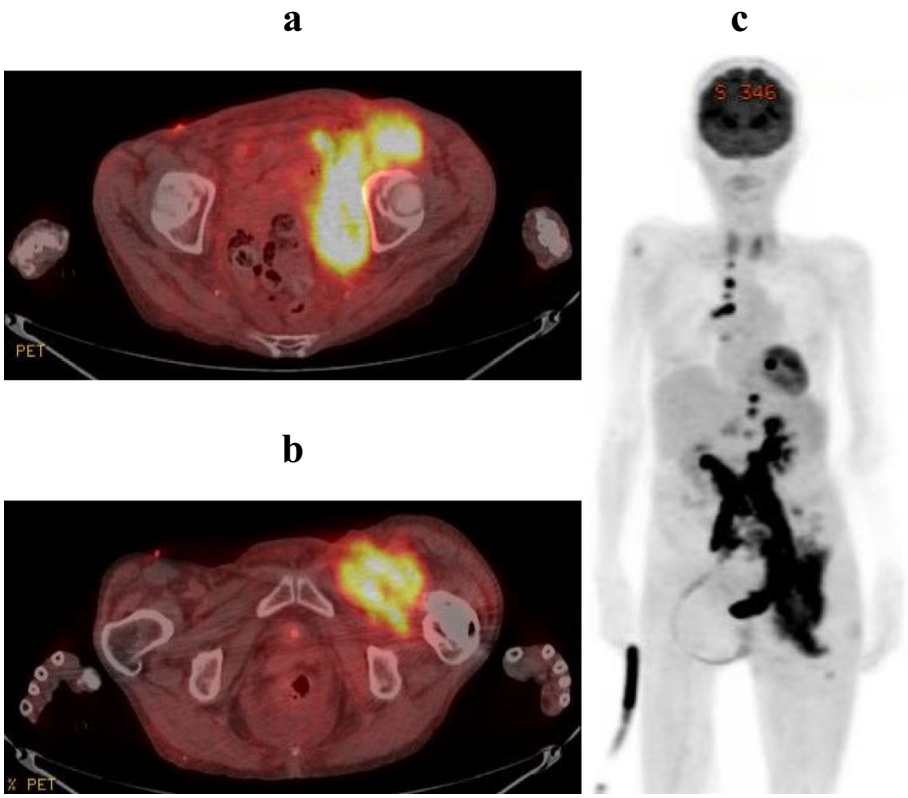

Figure 1. PET imaging with FDG showed an increased FDG uptake in the left iliopsoas (a, b). In addition to the iliopsoas muscle, the para-aortic LN, right hilar LN, and juxta-esophageal LN showed an FDG abnormal accumulation (c).

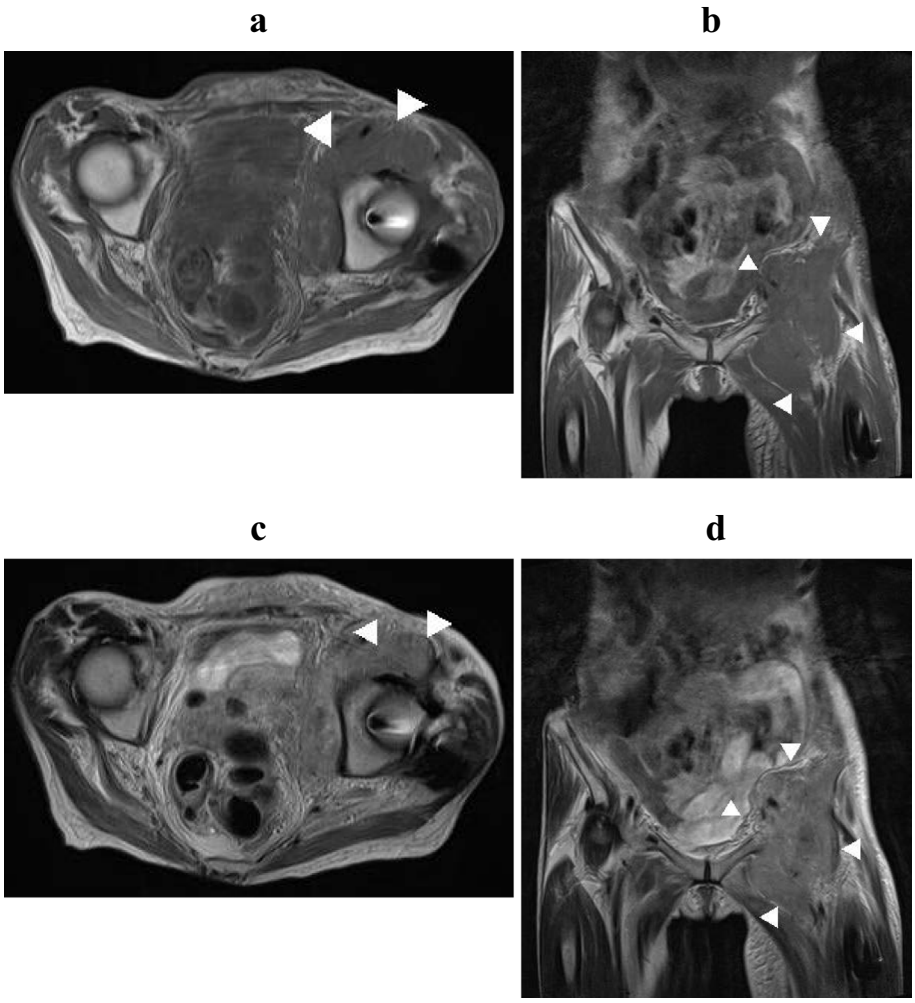

Figure 2. MRI findings. On T1-weighted (T1w) images, PSML had a similar signal intensity to muscle (a, b). On T2-weighted (T2w) images, the signal intensity of PSML was moderately increased compared to muscle (c, d).

jected because of her poor general condition and severe complications. She was therefore administered PSL 40 mg/day (1 mg/kg/day) for pain relief, causing the LDH level to temporarily decrease. Later, she experienced a rapid fatal course and died of multiple organ failure on day 19 of hospitalization. A post-mortem examination was subsequently performed with the consent of the patient's family.

Autopsy findings

At the autopsy, the patient showed swelling of the paraaortic LN, right hilar LN, periesophageal LN, hepatomegaly (weight=1,430 g), and splenomegaly (weight=150 g), in addition to the left iliopsoas tumor and left inguinal lymphadenopathy. Immunohistochemical staining of the left inguinal LN, which was not a major lesion, revealed lymphoma cell populations positive for CD2, CD3, CD4, CD30, PD-1, TIA 1, and granzyme B and negative for CD5, CD8, CD10, CD 20, CD56, and ALK. Nuclear staining demonstrated the presence of Ki-67 in approximately 80% of the cells (Fig. 3a-h). In the left iliopsoas tumor, there was diffuse proliferation of lymphoma cells, including CD3(+), CD5(-), CD20(-), and p53(+), and approximately 80% of the cells were positive for Ki-67 (Fig. 4a-d). In the spleen, the tumor cells were CD3(+), CD20(-), and Epstein-Barr encoding region *in situ* hybridization (EBER-ISH) (-) (Fig. 4e-h). Monoclonal rearrangement of the T-cell receptor beta chain genes on the DNA-extracted specimen obtained via Southern blotting was found in the left iliopsoas tumor, left inguinal LN, and right hilar LN. A chromosomal aberration analysis (G-banding) revealed growth failure in any specimen. The overall findings supported the definitive diagnosis of PTCL, NOS. Furthermore, although this case showed lymphoma cell infiltration of multiple LNs, the resultant LN enlargement was slight. We believe that the main lesion was the bulky iliopsoas mass. We ultimately diagnosed her disease as PSM-PTCL, NOS.

Discussion

A few large-scale, single-center studies have reported that the incidence rate of PSML was 0.11% (1)-0.21% (9) among all malignant lymphomas. Yang et al. reported that 6 of 8 PSML cases were DLBCL, while 1 of the remaining 2 was anaplastic large cell lymphoma, and the other was

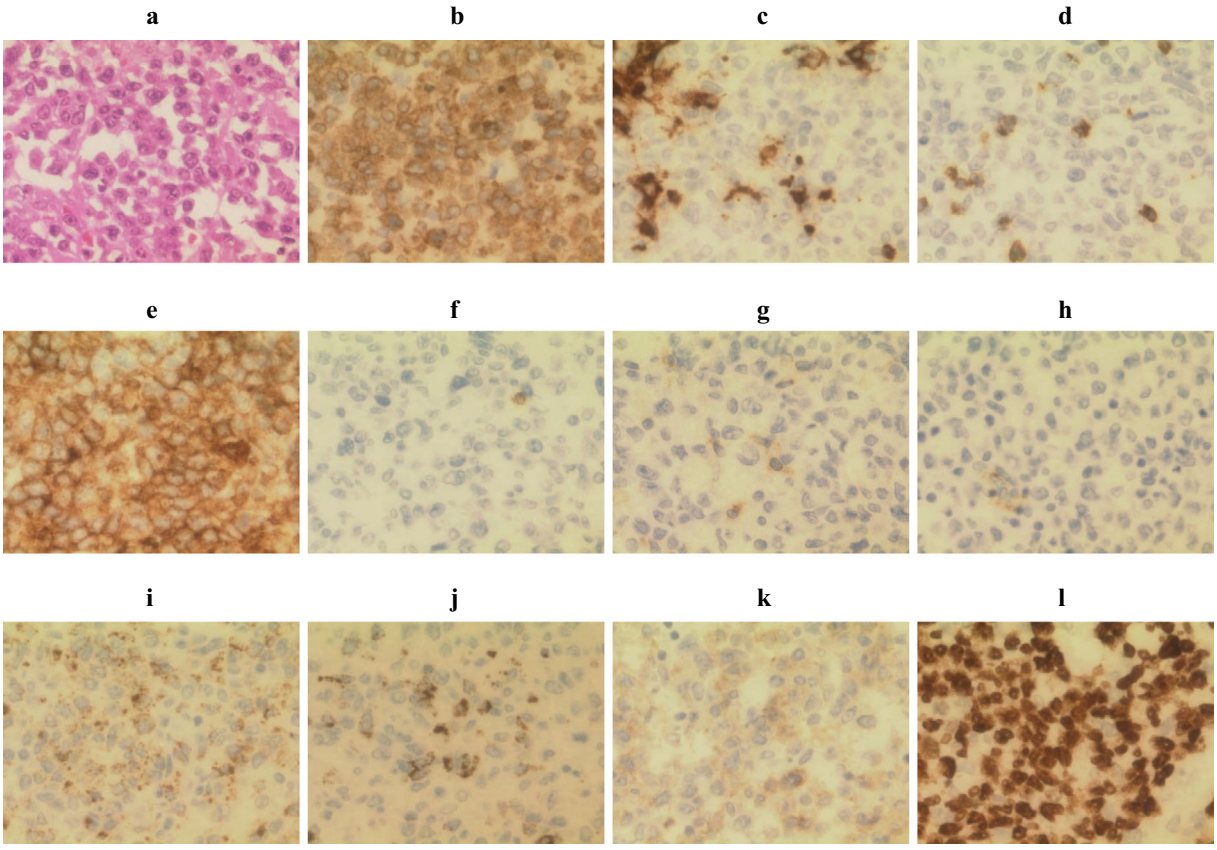

Figure 3. **Immunohistochemistry of PTCL, NOS of the left inguinal LN. Hematoxylin and Eosin staining, original magnification ×400 (a), tumor cells were CD3-positive (b), CD20-negative (c), CD5-negative (d), CD4-positive (e), CD8-negative (f), CD30 focally weakly positive (g), CD56-negative (h), TIA-1 focally positive (i), Granzyme B partially positive (j), and PD-1 weakly positive (k). Ki-67 staining showed a proliferation index of approximately 80% (l).**

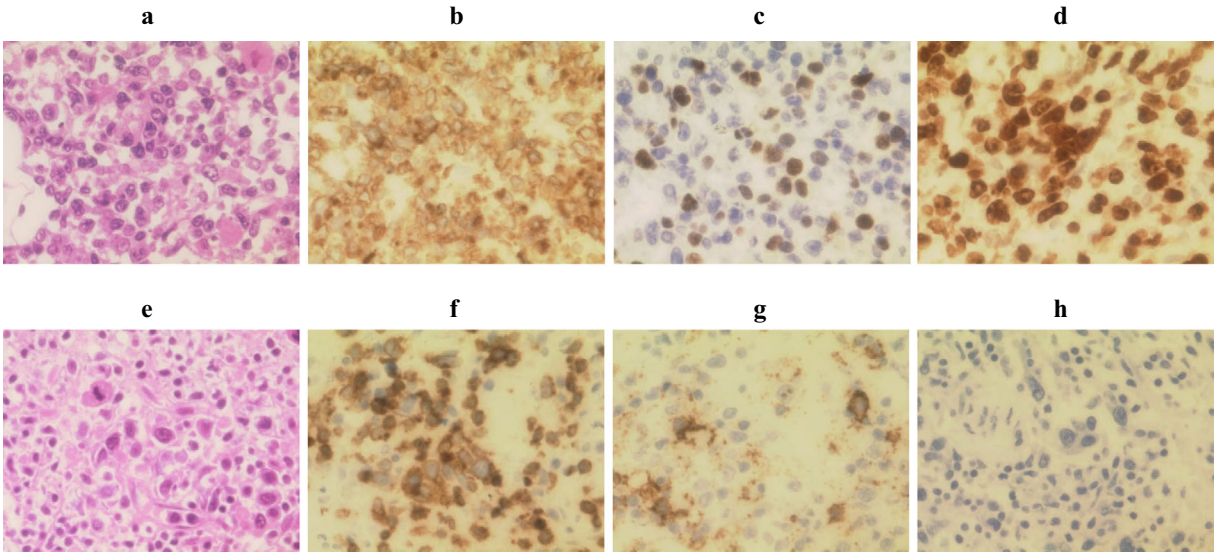

Figure 4. **Immunohistochemistry of PTCL, NOS of the left iliopsoas tumor and spleen. Diffuse proliferation of large lymphocytes in the left iliopsoas and spleen (a, e, Hematoxylin and Eosin staining, original magnification ×400). The upper part (a-d) is the iliopsoas tumor, and the lower part (e-h) is the spleen. Tumor cells are CD3-positive (b, f) and p53-positive (c). Ki-67 staining showed a proliferation index of approximately 80% (d). In the spleen, tumor cells were CD20-negative (g) and EBER-ISH-negative (h).**

Table 2. Clinical Features and Imaging Findings of Patients with PSM-PTCL, NOS.

Case	Age/ sex	PH	PS	Location	BM involve-ment	LDH (IU/L)	PIT group	Rhabdo-myolysis	MRI		Treatment	Outcome	Refer-ence
									T1	T2			
Our case	**71/F**	**SSc, PAH, femoral trochanteric fracture**	**4**	**iliopsoas**	**-**	**2,129**	**4**	**-**	**iso**	**high**	**prednisolone**	**died 19 days after admission**	**-**
1	23/F	healthy	4	psoas	-	356	3	-	NA		-	died 26 days after admission	2
2	56/M	healthy	0	sartorius muscle	-	normal	1	-	high	NA	CHOP ×6→ PBSCT	disease free for 1 year	3
3	49/F	NA	0	soleus muscle	-	NA	NA	-	iso	high	chemotherapy	disease free for 3 years	4
4	32/M	NA	1	quadratus lumborum	+	590	3	+	NA		CHOEP ×2	Alive	5
5	40/M	NA	0	trapezius muscle	-	NA	NA	-	NA	high	CHOP ×6	disease free for 6 months	6
6	62/M	DM, HT	2	psoas	-	NA	NA	+	NA		chemotherapy	disease free for 6 months	7
7	43/M	healthy	1	quadriceps muscle	-	6,655	2	-	NA		CHOP ×6	disease free for 2 years	8
8	28/F	healthy	0	sternocleidomastoid	-	NA	NA	-	NA		surgery→ CHOP	disease free for 4 years	9

F: female, M: male, NA: not available, PH: past history, SSc: systemic sclerosis, PAH: pulmonary arterial hypertension, DM: diabetes mellitus, HT: hypertension, PS: performance status, BM: bone marrow, PIT: Prognostic Index for PTCL-U, CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone (E, etoposide), PBSCT: peripheral blood stem cell transplantation

PTCL, NOS (9). The average age was 54.8 (range 23-76) years old, which was relatively young. The most common sites of tumors were the extremities, especially the lower extremities, including the quadriceps femoris, iliopsoas, and buttocks. The pathogenesis of lymphoma arising in the musculature is unclear; however, PSML is thought to occur in lymphoid infiltrates induced by chronic inflammation in extranodal sites (12). Several reports have described the development of lymphoma at sites of previous injuries or drug injections (13). In our case, a screw had been inserted in the left femur for the surgical treatment of peritrochanteric femur fracture. We suspect that the surgical history in the present patient was related to the development of PSML.

Eighty percent of PSML cases are histologically confirmed to be B-cell lymphoma (14). There have only been 8 previous reports on PSM-PTCL, NOS (Table 2). Six of the patients (75%, 6/8) were under 50 years old at the time of the diagnosis, and most patients had no remarkable history. Our patient was 71 years old, making her the oldest patient reported thus far, and she had a history of SSc and PAH. Our patient's background differed from those of other PSM-PTCL, NOS patients. We predicted from case presentation that almost cases had good performance status, except for the two cases with rhabdomyolysis (No. 4 and 6) and the case with massive infarction caused by dissemination of the lymphoma cells (No. 1). The Prognostic Index for PTCL-U (PIT) (15), which is a specific prognostic model of PTCL-U, showed that 3 (60%, 3/5) cases were classified into groups 3 and 4. PIT groups 3 and 4 of PTCL-U have a poor prognosis, with a 5-year survival probability of just 26.8%. Furthermore, we suspected the present patient would have a dismal prognosis due to the extranodal subtype; however, surprisingly 7 (87.5%, 7/8) previous cases of PSM-PTCL, NOS responded to cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP)-like chemotherapy. It was suggested that "primary skeletal muscle" PTCL, NOS might possesses different oncogenicity from common "nodal" PTCL, NOS. Interestingly, a previous meta-analysis of published series reported that despite the poor prognosis of nodal T-cell lymphomas, the outcome of patients with primary soft tissue T-cell lymphomas was more favorable than that of patients with primary soft tissue DLBCL (16).

According to the WHO classification, OIIA-LPD is defined as lymphoid proliferations or lymphoma that develop in patients receiving immunosuppressive drugs for autoimmune diseases (11). Our case was categorized as OIIA-LPD owing to her 24-year history of receiving CyA for SSc. Patients with autoimmune diseases naturally have a high incidence of malignant lymphoma (ML) compared with the general population. A number of case reports and series have highlighted the association between SSc and ML, and a literature review concluded that the association of SSc and ML might not be coincidental (17). In addition, immunodeficiency due to disease and immunosuppressive drugs promotes the development of ML. Several studies have reported the development of OIIA-LPD in patients receiving immunosuppressive drugs other than methotrexate (MTX). For example, Ichikawa et al. reported that 17 (17%) patients had non-MTX-LPD among 102 patients with OIIA-LPD (18). In a previous report, ML was detected in rheumatoid arthritis

Table 3. Immunohistochemistry Findings of Patients with PSM-PTCL, NOS.

Case	CD2	CD3	CD4	CD5	CD8	TIA-1	Granzyme B	CD30	EBER-ISH	p53	Ki-67
Our case	**+**	**+**	**+**	**-**	**-**	**+**	**+**	**Weak+**	**-**	**+**	**80%**
1	NA	+	+	+	-	NA	NA	-	NA	NA	10%
2	NA	+	+	+	-	NA	NA	-	NA	NA	NA
3	NA	+	-	-	-	NA	NA	-	-	NA	NA
4	+	+	NA	+	NA	NA	+	-	-	NA	60-70%
5	NA	+	-	-	+	NA	NA	NA	-	NA	NA
6	+	+	+	-	+	+	+	-	-	NA	NA
7	NA	+	NA	NA	NA	NA	NA	-	-	NA	NA
8	NA	+	NA	NA	NA	-	NA	-	-	NA	NA

NA: not available, TIA-1: T cell intracellular antigen 1, EBER-ISH: Estein-Barr virus-encoded RNAs detected by in situ hybridization

patients (19); therefore, the effects of CyA leading to ML development need to be carefully monitored, regardless of the duration of CyA treatment, but especially in those undergoing long-term treatment. The major types of OIIA-LPDs are DLBCL and HL, comprising 58% and 15.3% of 274 cases of OIIA-LPD, respectively (11). T-LPD is uncommon, and a recent report by Satou et al. reported that only 6 (13.9%, 6/43) patients were subclassified as PTCL, NOS among a total of 43 cases of T-LPD. Furthermore, only 5 (11.6%, 5/43) patients had primary extranodal lymphoma, while there were no patients with PSML (20). Several subtypes of OIIA-LPD have a high Epstein-Barr virus (EBV)-positivity; however, a previous report revealed that patients with T-LPD had a significantly lower proportion of EBV-positive tumor cells than those with B-LPD (18). In our case, where non-MTX T-LPD was also EBER-ISH-negative, we suspected that the mechanisms underlying tumorigenesis did not involve EBV reactivation.

On comparing the histopathologic features of the previous eight cases of PSM-PTCL, NOS and our own, our patient seems to have distinct clinicopathologic features, such as being positive for cytotoxic markers (TIA-1, Granzyme B) and p53-positive, having a high Ki-67 index, and being weakly positive for CD30 (Table 3). Unfortunately, immunohistochemical studies of the previous PSM-PTCL, NOS cases were performed with limited staining. Therefore, it was difficult for us to describe the clinicopathological features of this rare disease entity, PSM-PTCL, NOS. Among them, we focused on p53, especially regarding tumorigenicity. The *TP 53* gene is an important tumor suppressor gene, and a *TP53* mutation is involved in the events of tumorigenesis, being present in a variety of cancer subtypes. A previous report demonstrated a positive correlation between *TP53* mutation and p53 expression in PTCL using next-generation sequencing and immunohistochemical staining patterns (21). p53 overexpression was observed in 19.6% (11/56) of peripheral mature T and NK cell lymphomas, indicating an extremely poor prognosis. PTCL is a heterogeneous group, and PTCL, NOS is a wastebasket category with broad morphological and immunophenotypic characteristics. However, a recent study demonstrated distinct genetic profiles in these subtypes of PTCL, NOS. Two major defined molecular subtypes of PTCL-NOS include PTCL-GATA3 and PTCL-TBX 21, which have distinct biological differences in oncogenic pathways and prognoses (22). PTCL-GATA3 showed a worse overall survival and more aberrant genome expression than PTCL-TBX21. *TP53* mutations were associated with PTCL-GATA3; thus, aberrant *TP53* signaling due to a mutation was significantly associated with PTCL-GATA3 ($p< 0.001$), and *TP53* functional impairment may lead to distinct clonal evolution (23). We considered the overexpression of p 53 to likely be associated with an aggressive clinical course and high-grade oncogenicity.

In conclusion, we reported the first case of PSM-PTCL, NOS, and OIIA-LPD. It was suggested that the cause of the rapid fatal course in this case, unlike previous cases of PSM-PTCL, NOS, was a combination of patient immunodeficiency and high-grade oncogenicity of the tumor, reflected by the positive p53 expression. The clinical and pathologic characteristics are neither consistent nor clear. Gene expression profiling studies may increase our understanding of the molecular pathogenesis of this rare entity, PSM-PTCL, NOS.

Informed consent was obtained from the family of the patient for allowing both the post-mortem examination and tt publication of this study.

The authors state that they have no Conflict of Interest (COI).

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