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【 CASE REPORT 】

Magnetic Resonance Imaging-negative, Rituximab-resistant Neurolymphomatosis as a Paradoxical Presentation of Relapsed Primary Adrenal Lymphoma

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Abstract:
Primary adrenal lymphoma (PAL) is rare and known to have a predilection for central nervous system (CNS) relapse. A 70-year-old man with a 2-year history of primary aldosteronism presented because of a fever. He was hypotensive, and his adrenal glands were unequivocally enlarged. PAL was diagnosed. Despite showing an initial response to immunochemotherapy, progressive paralysis ensued. Magnetic resonance imaging findings were negative, and rituximab was ineffective. His debilitated condition hindered further chemotherapy. A postmortem examination revealed lymphoma relapse in the systemic peripheral nerves. The sequential presentation of two rare lymphomas implies that PAL might have a predilection for not only the CNS but also peripheral nerves.

Key words: neurolymphomatosis, primary adrenal lymphoma, diffuse large B-cell lymphoma

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Introduction

Diffuse large B-cell lymphoma (DLBCL) arise primarily from extranodal sites in about 30% of cases (1, 2). Extranodal involvement is a poor prognostic indicator according to the International Prognostic Index score, a commonly used prognostic tool in patients with DLBCL (3). Certain specific anatomical sites of extranodal involvement are also associated with a poorer outcome, including bone marrow, central nervous system (CNS), liver, gastrointestinal tracts and lungs (2), and these sites were incorporated in a recent prognostic stratification of DLBCL, such as NCCN-IPI (4). However, the site-specific prognostic implication of infrequent extranodal lymphomas is not always clear, as their low incidence in surveillance studies may hinder recognition of any statistical significance concerning the prognosis (2).

The incidence of primary adrenal lymphoma (PAL) is extremely low, although secondary involvement in the adrenal glands has been described as a relapsed site of DLBCL or as a disseminated lesion of intravascular large B-cell lymphoma without organ specificity (5). Previous studies have suggested that PAL may also follow an aggressive clinical course with its predilection for dissemination into the CNS, although the absolute risk of nervous involvement of extranodal lymphomas in general is still being debated (5, 6).

Neurolymphomatosis (NL) is another rare extranodal lymphoma with a nerve-seeking manifestation, disseminating primarily into the peripheral nerves (7, 8). Although the affected patients commonly present with neuralgia in the involved sites, the definitive diagnosis of NL may often be delayed, since the presenting symptoms are highly variable and a wide range of differential diagnoses must be ruled out, including therapy-related neuropathy (9). Imaging studies, such as magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET), may alert clinicians to the affected sites and guide a biopsy for the pathological diagnosis (10, 11). However, the

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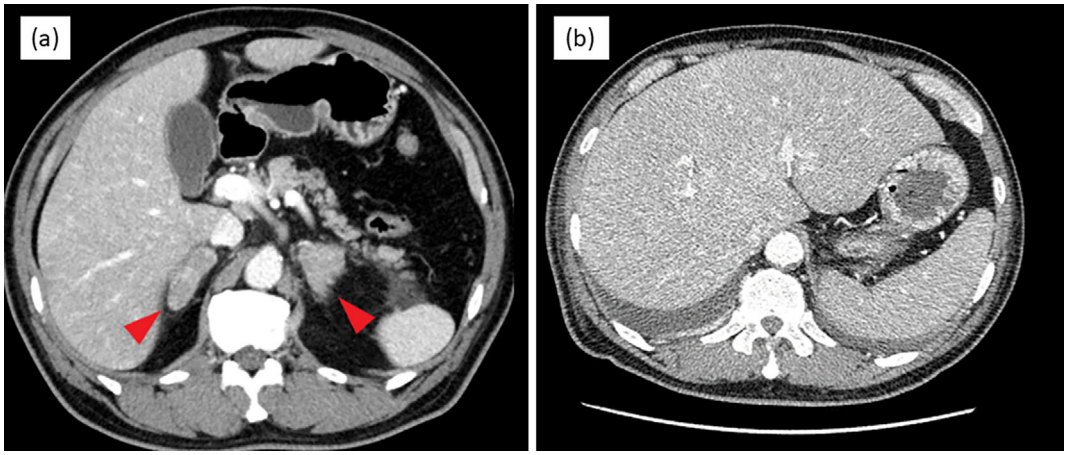

Figure 1. Computed tomography (CT) at presentation revealed bilateral enlargement of the adrenal glands (arrowheads) (a). There was hepatosplenomegaly (b), but no ascites was noted.

highly invasive nature of a peripheral nerve biopsy as well as the highly progressive clinical course of NL may often preclude the timely diagnosis and implementation of treatment. Indeed, it is not uncommon for NL to be diagnosed by a postmortem examination (8).

We herein report a case with a sequential presentation of two rare extranodal lymphomas (PAL and NL). The present case merits reporting not only because it implies a novel insight for the anatomical pattern of disease relapse of PAL but also because it may suggest a sanctuary nature of peripheral nerves.

Case Report

A 70-year-old man presented to a tertiary university hospital because of a 3-month episode of a fever of unknown origin. He had had a history of primary aldosteronism with a unilateral adrenal mass on the right side requiring antihypertensive agents for the past two years. Three months prior to the presentation, the patient started to complain of malaise, chills and a fever, which had persisted and compromised his general well-being.

The laboratory tests at the referring hospital showed anemia, thrombocytopenia and an elevated level of lactate dehydrogenase (LDH). Computed tomography (CT) revealed bilateral enlargement of the adrenal glands and hepatosplenomegaly (Fig. 1). He was admitted to the university hospital under suspicion of primary adrenal lymphoma (PAL).

At presentation, he had a fever of over 39℃, heart rate of 122 beats per minute and blood pressure of 91/56 mmHg even after cessation of the antihypertensive drugs. The superficial lymph nodes were not palpable, and distention of the abdomen and pretibial pitting edema were noted on a physical examination. CT revealed no nodal diseases, but its cross section showed that the adrenal glands were 4.3 cm×1.6 cm (right) and 4.0 cm×2.5 cm (left) in size, and the spleen was 12.5 cm×3.6 cm in size.

The laboratory data showed deteriorated anemia, thrombocytopenia, increased LDH and elevated soluble interleukin-2 receptor. Aldosterone was below the lower limit of normal (Table). A random skin incisional biopsy from the chest, abdomen and thighs, showed that he had no lymphomatous infiltrations, including the subcutaneous vasculature (Fig. 2). A bone marrow biopsy revealed diffuse proliferation of large-sized atypical lymphoid cells. Immunohistochemistry showed positivity for CD20, bcl-6 and MUM-1 and negativity for CD5 and CD10. However, anti-CD34 staining revealed no intravascular infiltration (Fig. 3). EBV *in situ* hybridization was negative. Intravascular lymphoma was ruled out, and extranodal DLBCL, non-germinal center (non-GC) type, was diagnosed.

A transjugular liver biopsy was also performed, and proliferation of similar lymphoid cells was found. Although a CT-guided adrenal biopsy was planned, it was withheld because the urgent need for treatment outweighed the need for another confirmatory invasive procedure. Since the bilateral adrenal lesions were deemed dominant compared to other nodal and extranodal lesions, the bilaterally enlarged adrenal glands were considered to be the primary sites of involvement.

Immunochemotherapy with cyclophosphamide, doxorubicin, vincristine (VCR), prednisolone and rituximab was started soon after the diagnosis, which was complicated with tumor lysis syndrome, disseminated intravascular coagulation with splenic hemorrhaging and congestive heart failure. The splenic hemorrhaging required catheter intervention. The laboratory data, such as the abnormal LDH, liver enzymes and DIC parameters, returned to the reference range of normal about two weeks after the administration of rituximab, implying that the first course of the R-CHOP-like regimen had been effective. The clinical course is depicted in Fig. 4.

At 42 days after admission (2 weeks after the completion of the R-CHOP-like therapy), however, the patient started to experience bilateral neuralgia in the upper and lower extremities. Although this neurological symptom was symmetrical, as in the VCR-induced peripheral neuropathy, it devel-

Table. Laboratory Data at Admission.

Blood Counts		Immunochemistry	
WBC	3.19×10^3 /μL	TP	4.5 g/dL
SEG	65 %	ALB	1.7 g/dL
BND	16 %	BUN	18.8 mg/dL
MON	8 %	Cre	1.04 mg/dL
LYM	9 %	AST	98 U/L
UNC	2 %	ALT	40 U/L
RBC	3.09×10^6 /μL	γGT	50 U/L
Hb	8.5 g/dL	T-Bil	1.15 mg/dL
PLT	2.8×10^4 /μL	ALP	533 U/L
		LDH	586 U/L
Hemostasis		CRP	9.84 mg/dL
PT	35 s	Ferritin	1,853 ng/mL
APTT	40.1 s	sIL-2R	13,157 U/mL
FDP-DD	8.9 μg/mL	COR	24.1 μg/dL
FIBG	236 mg/dL	ALD	<25.0 pg/mL
		ACTH	8.2 pg/mL

WBC: white blood cell, SEG: segmented neutrophil, BND: band neutrophil, MON: monocyte, LYM: lymphocyte, UNC: unclassified cell, RBC: red blood cell, Hb: hemoglobin, PLT: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, FIBG: fibrinogen, TP: total protein, ALB: albumin, BUN: blood urea nitrogen, Cre: creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGT: γ-glutamyl transpeptidase, T-Bil: total bilirubin, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, COR: cortisol, ALD: aldosterone, sIL-2R: soluble interleukin-2 receptor, ACTH: adrenocorticotropic hormone

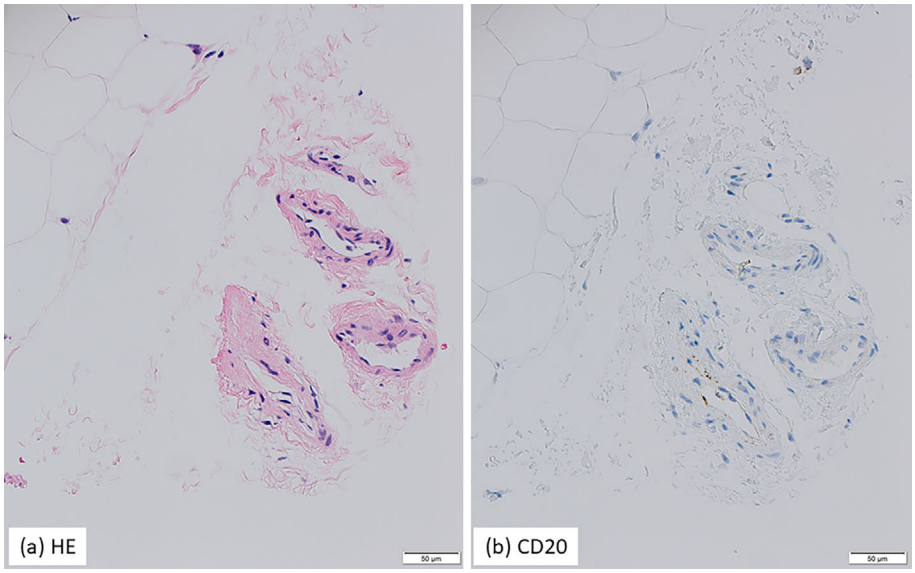

Figure 2. A random skin incisional biopsy revealed no lymphomatous infiltration in the vasculature, with similar findings on (a) Hematoxylin and Eosin staining and (b) CD20 preparations.

oped more proximally and progressed rapidly. While NL was also suspected, his general condition with a very poor performance status precluded further administration of cytotoxic agents. He instead received a second cycle of rituximab on day 43, but his neurologic impairment deteriorated further during the following weeks. He became quadriplegic around day 50, and dysarthria, dysphagia and diplopia also ensued.

Plain MRI of the spinal cord and the brachial plexus on day 40 revealed that he did not have any compressing mass lesions nor any enlargement in the nerve fibers (Fig. 5). Another MRI scan of the brain on day 48 revealed no cerebral disease, but a small lesion was noted in the pons with a high intensity in T2-weighted imaging, which was compatible with central pontine myelinolysis (Fig. 6). The laboratory data, however, revealed no apparent electrolytic imbal-

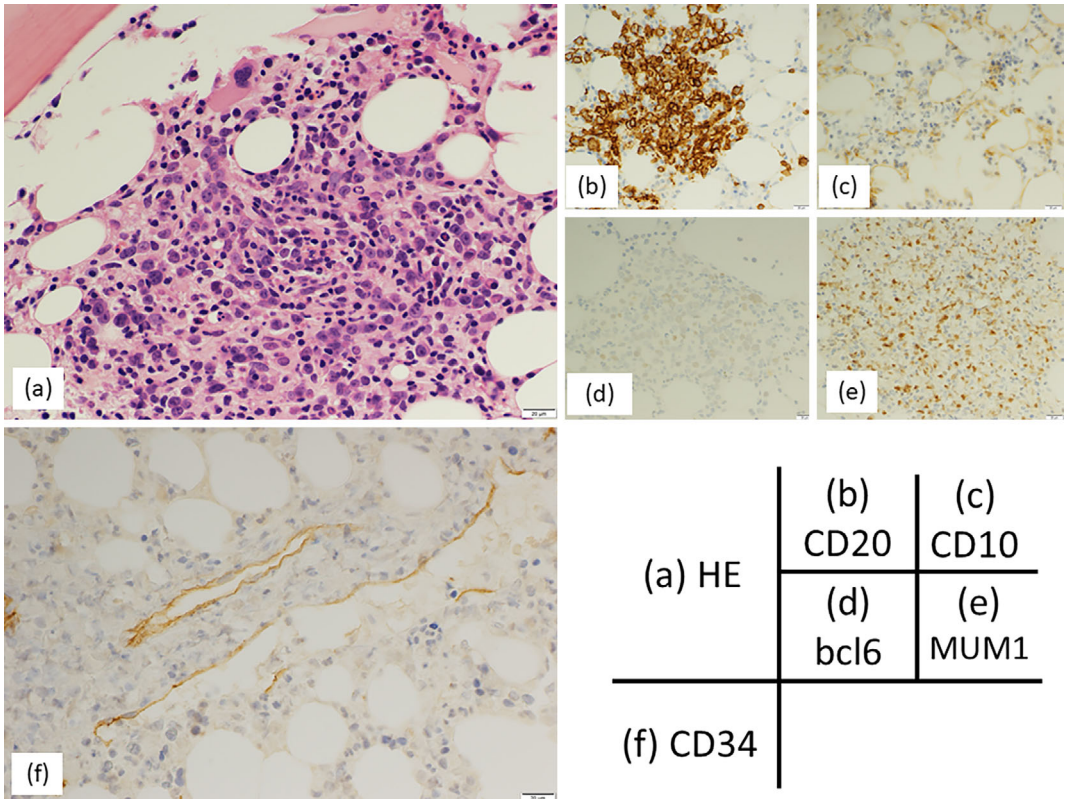

Figure 3. **A bone marrow biopsy showed infiltration of lymphoma cells. (a) Hematoxylin and Eosin staining showed diffuse proliferation of large-sized lymphoma cells. They were CD20-positive (b) and CD10-negative (c) findings. Both bcl-6 (d) and MUM-1 (e) were positive. CD34 staining revealed no intravascular infiltration of lymphoma cells (f). According to the Hans classification, diffuse large B-cell lymphoma, non-GC type, was diagnosed.**

ance. Another brain MRI scan on day 55 and 67 showed amelioration of the pontine lesion. A cerebrospinal fluid examination showed total protein 178 mg/dL, glucose 108 mg/dL and increased mononuclear cells (87 cells/μL), most of which were T-cells with class-III cytology. The patient ultimately died from aspiration pneumonia on day 77.

A postmortem examination revealed large-sized lymphoma cells infiltrating the systemic peripheral nerve fibers, including bilateral sympathetic nerves, bilateral brachial plexuses and nerve roots at C5, C7 and C8 (Fig. 7). Group atrophy was found in the iliopsoas and other skeletal muscles adjacent to the lumber plexuses. Lymphomatous infiltration was also observed in the perivascular areas and subpleural areas of the lungs and the Glisson sheath in the hepatoduodenal ligament, mesentery and other connective tissues. The right adrenal gland showed remnants of lymphoma cells and adenoma. No lymphomatous involvement was observed in the bone marrow or CNS. Local gliosis with edema was observed at the central pons, which was compatible with the pathological changes of central pontine myelinolysis. The spleen had a 3-cm hematoma, but there was no lymphomatous infiltration. Intravascular lymphoma was not detected in any organs. Nodal lesions were not detected. The residual lymphoma cells showed identical immunophenotypes to those at the presentation. Neurolymphomatosis as relapsed disease of PAL was thus confirmed.

Discussion

PAL is defined as having the following: (a) adrenal gland involvement, (b) no history of lymphoma elsewhere and (c) adrenal lesions unequivocally dominant if there are other nodal/extranodal lesions (5). In the present case, an adrenal biopsy was withheld at the discretion of the physicians, as the need to promptly implement chemotherapy outweighed the need for another confirmatory biopsy with its procedural risks. Despite the lack of a biopsy of the glands, however, the present case was still considered to have PAL because of the glands' dominant size with bilaterality, the pathological diagnosis of extranodal DLBCL being established with the concurrent bone marrow and liver biopsies and the subsequent adrenal response to immunochemotherapy.

Rashidi et al. described some of the demographic, clinical and pathological features commonly found in 187 cases with PAL (5). Among the common features described, B symptoms and a high LDH level as well as bilaterality of adrenal lesions were also found at the presentation in the present case. Adrenal insufficiency at the presentation was another frequent characteristic, being shared by 60% of cases with PAL in previous studies (5, 12). However, the present case was preceded by a two-year history of primary aldosteronism, which was a rather atypical presentation for PAL.

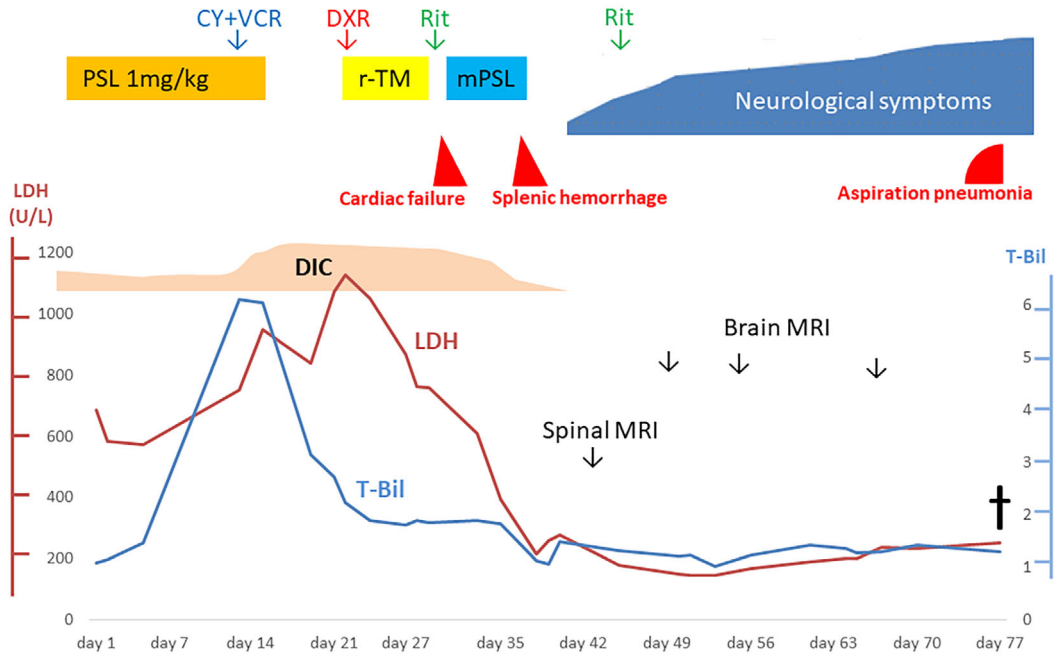

Figure 4. **The clinical course. After R-CHOP-like chemotherapy was administered, the abnormal laboratory data, including total bilirubin and LDH, were ameliorated. Although the treatment was complicated with tumor lysis syndrome, disseminated intravascular coagulation with splenic hemorrhaging and cardiac failure, the primary adrenal lymphoma seemed to respond well to the chemotherapy. Soon after the recovery from the complications, however, the patient experienced bilateral neuralgia and progressive paralysis in the limbs, and bulbar paralysis ensued. While neurological signs and symptoms deteriorated, the level of LDH stayed within the upper limit of the reference range of normal, and no other nodal/extranodal lymphoma lesions were observed. The neurological symptoms seemed to have evolved during an on-going response to the chemotherapy outside of the peripheral nerves. CY: cyclophosphamide, VCR: vincristine, DXR: doxorubicin, Rit: rituximab, r-TM: recombinant thrombomodulin, LDH: lactate dehydrogenase**

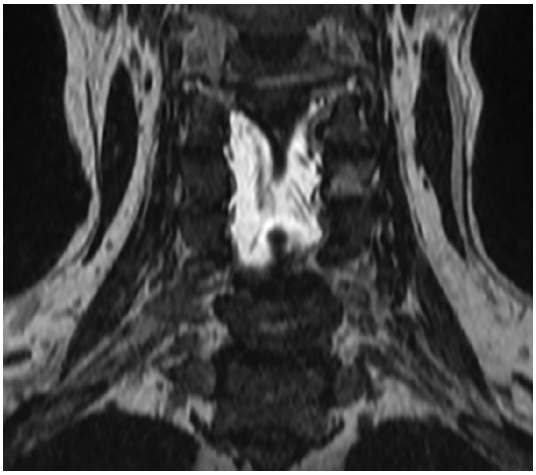

Figure 5. **Plain MRI of the brachial plexus on day 40 showed that he had no compressing mass lesions and no enlargement in the nerve fibers.**

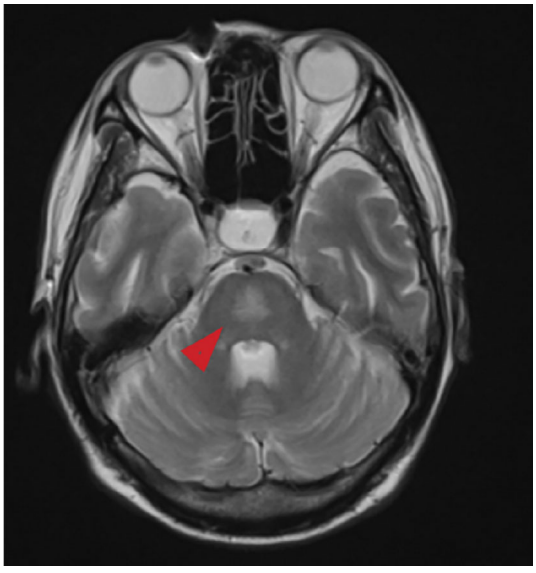

Figure 6. **Brain MRI showed a high intensity on T2-weighted imaging in the pons (arrowhead).**

Such a functional transition of the adrenal glands from a hypertensive to hypotensive state in a short period of time might have been the result of a pathological change in the glands of the present case, with a functional benign adenoma potentially being overridden by an unfunctional highly aggressive lymphoma.

Neurolymphomatosis frequently poses a diagnostic dilemma, as it may often present as an isolated neuropathy

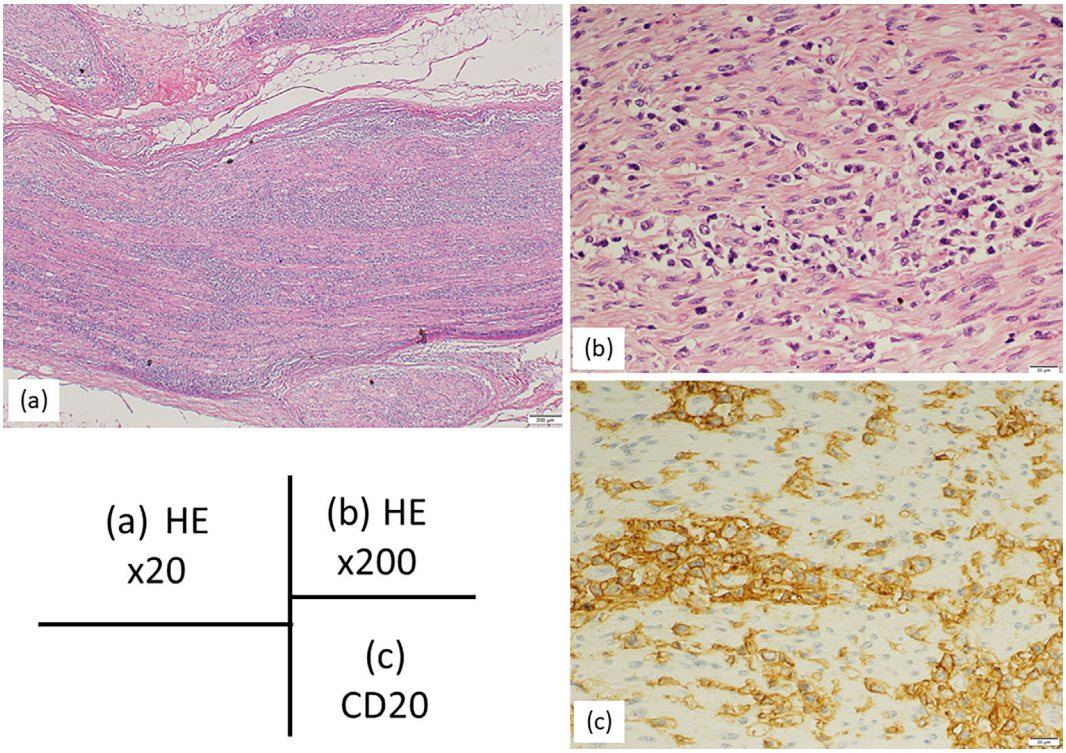

Figure 7. **The postmortem examination revealed neurolymphomatosis. Hematoxylin and Eosin staining of the brachial plexus showed large lymphoma cells infiltrating into the nerve fibers, ×20 (a) and ×200 (b). The lymphoma cells were CD20-positive (c).**

without other overt lymphomatous development (10). One of the most remarkable features of the present case was that the NL, as a relapsed disease, had developed during a seemingly ongoing response to chemotherapy at other anatomical sites. Because the initial presentation of NL occurred shortly after the previous round of chemotherapy for PAL, it was a diagnostic challenge to rule out other possible differential diagnoses, such as demyelinating polyneuropathies, VCR-induced neuropathy and virus-associated neuropathy (9, 10).

Imaging studies, such as MRI and FDG-PET, may alert clinicians to affected sites and facilitate the timely diagnosis and intervention, although the suboptimal sensitivity and specificity of these modalities have also been described (10, 11). Indeed, 45% of NL cases were not diagnosed until a postmortem examination, according to a previous review that included case reports published before the introduction of FDG-PET (8). In the present case, non-enhanced MRI of the brachial plexus did not reveal any compressing lesions, enlargement or laterality in the nerve fibers while the bilateral neuropathy was developing aggressively. The unavailability of FDG-PET in the present case might have been part of the reason a pre-mortem diagnosis of neurolymphomatosis was quite challenging. Enhanced MRI or FDG-PET might have been helpful for identifying the localization of peripheral nerve involvement, and their performance should be encouraged when indicated.

Abe et al. summarized the brain MRI changes of 33 patients with intravascular lymphoma and found that hyperintense lesions in the pons were present in 57% of patients, which might have diagnostic implications (13). In the present case, a similar pontine lesion was found on MRI near the onset of neurolymphomatosis, although intravascular lymphoma was ruled out during the initial diagnostic workup for PAL and the autopsy. Such pontine lesions might also be pertinent to PAL and neurolymphomatosis.

Of note: the paradoxical response to immunochemotherapy encountered in the present case may not be exceptional for NL (9, 11). Indeed, such a response or treatment resistance of NL seems to be in accordance with the presumed notion that a blood-peripheral-nerve barrier might have prevented the penetration of immunochemotherapeutic agents, as the blood-brain barrier does, making the peripheral nerves sanctuary sites (11).

This is the first case report to describe a peripheral nervous relapse of PAL. While rare, PAL is a nerve-seeking lymphoma, and more than 10% of cases have been previously reported to relapse in CNS (5). The present case is unique in that the neurolymphomatosis was isolated nervous involvement of PAL without CNS disease. Intravascular lymphoma is another nerve-seeking lymphoma that tends to develop as CNS disease as a result of systemic spread, and the biological similarity between primary CNS lymphoma and intravascular lymphoma has been described (1). However, data on the biological and immunophenotypic associations between NL and PAL are lacking. The sequential presentation of two extremely rare extranodal lymphomas (PAL and NL) in the present case might highlight the possible predilection of PAL for peripheral nerves as well. Because

of the time-consuming nature of the accrual of extremely rare extranodal lymphomas like the present case, an analysis of the genetic-phenotypic associations might facilitate our understanding of the site-specific biology and prognosis of PAL and NL.

In summary, this is the first case report of peripheral nervous relapse of PAL. The sequential presentation of the rare extranodal lymphomas PAL and neurolymphomatosis may support novel insight into the anatomical pattern of disease relapse of PAL as well as the sanctuary nature of peripheral nerves.

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

References

1. Ollila TA, Olszewski AJ. Extranodal diffuse large B cell lymphoma: molecular features, prognosis, and risk of central nervous system recurrence. Curr Treat Options Oncol **19**: 38, 2018.
2. Castillo JJ, Winer ES, Olszewski AJ. Sites of extranodal involvement are prognostic in patients with diffuse large B-cell lymphoma in the rituximab era: an analysis of the Surveillance, Epidemiology and End Results database. Am J Hematol **89**: 310-314, 2014.
3. International Non-Hodgkin's Lymphoma Prognostic Factors P. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med **329**: 987-994, 1993.
4. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood **123**: 837-842, 2014.
5. Rashidi A, Fisher SI. Primary adrenal lymphoma: a systematic review. Ann Hematol **92**: 1583-1593, 2013.
6. Ferreri AJ. Risk of CNS dissemination in extranodal lymphomas. Lancet Oncol **15**: e159-e169, 2014.
7. Grisariu S, Avni B, Batchelor TT, et al. Neurolymphomatosis: an International Primary CNS Lymphoma Collaborative Group report. Blood **115**: 5005-5011, 2010.
8. Baehring JM, Damek D, Martin EC, Betensky RA, Hochberg FH. Neurolymphomatosis. Neuro Oncol **5**: 104-115, 2003.
9. Gan HK, Azad A, Cher L, Mitchell PLR. Neurolymphomatosis: diagnosis, management, and outcomes in patients treated with rituximab. Neuro-Oncology **12**: 212-215, 2009.
10. Bourque PR, Warman Chardon J, Bryanton M, Toupin M, Burns BF, Torres C. Neurolymphomatosis of the brachial plexus and its branches: case series and literature review. Can J Neurol Sci **45**: 137-143, 2018.
11. Matsue K, Hayama BY, Iwama K, et al. High frequency of neurolymphomatosis as a relapse disease of intravascular large B-cell lymphoma. Cancer **117**: 4512-4521, 2011.
12. Mozos A, Ye H, Chuang WY, et al. Most primary adrenal lymphomas are diffuse large B-cell lymphomas with non-germinal center B-cell phenotype, BCL6 gene rearrangement and poor prognosis. Mod Pathol **22**: 1210-1217, 2009.
13. Abe Y, Narita K, Kobayashi H, et al. Clinical value of abnormal findings on brain magnetic resonance imaging in patients with intravascular large B-cell lymphoma. Ann Hematol **97**: 2345-2352, 2018.