SPANDIDOS
PUBLICATIONS

Possible role of a malfunctioning immune system in discordant lymphoma with peripheral T-cell lymphoma secondary to classical Hodgkin lymphoma: A case report

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Abstract. The present case report investigated the clinicopathological features and potential mechanisms underlying the transformation to peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), following treatment for classical Hodgkin lymphoma (CHL) in a 73-year-old man. The patient was admitted to hospital in 2012 and underwent a left cervical lymph node biopsy, which confirmed CHL of the nodular sclerosing type, with evident bone marrow involvement. The patient received four cycles of doxorubicin, bleomycin, vinblastine and dacarbazine chemotherapy, after which they achieved complete remission. However, after 3 years, the patient presented with enlarged left inguinal lymph nodes and a biopsy revealed PTCL-NOS. Molecular studies indicated a T-cell receptor-γ gene rearrangement. A literature review, together with the current case, identified 11 patients with CHL that transformed into PTCL-NOS. Among these, nine patients (81.82%) were middle-aged or elderly (>45 years old), and eight (72.73%) experienced transformation within 3 years post-treatment of CHL. Among these eight patients, seven (87.50%) predominantly exhibited the nodular sclerosis subtype, with a median recurrence time of 26 months. Five (45.45%) patients died of the disease. The rare transformation of CHL to PTCL-NOS, primarily among men, underscores its clinical significance. Notably, nodular sclerosing-type CHL appears to be particularly prone to transformation into PTCL-NOS. The poor prognosis in such cases may be attributed to the complex tumor microenvironment of CHL.

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Introduction

Classical Hodgkin lymphoma (CHL), a malignancy of the lymphatic system, is one of the most prevalent types of lymphoma, exhibiting an incidence of 2-3 cases per 100,000 individuals annually in developed countries (1). It is generally regarded as a highly curable disease, especially with the use of standard first-line chemotherapy and, in some cases, radiotherapy (2). Peripheral T-cell lymphoma (PTCL) represents a group of aggressive non-Hodgkin lymphomas (NHLs) (3), among which, PTCL, not otherwise specified (PTCL-NOS), constitutes approximately one-third of all PTCL cases (4). PTCL-NOS is the most frequently encountered subtype of PTCL in North America and Europe, excluding Native Americans, accounting for ~30% of all PTCL diagnoses (5). These malignancies involve a heterogeneous collection of mature T-cell neoplasms, typically characterized by a complex clinicopathological presentation and an aggressive clinical course, leading to a poor prognosis (5,6). The coexistence of two or more types of lymphoma within the same or different organs is described as composite lymphoma or discordant lymphoma. The histological patterns are well-defined and clearly demarcated, often comprising two or three types of NHL or a combination of Hodgkin lymphoma (HL) with NHL (7). CHL originates from germinal center B lymphocytes (8) and PTCL-NOS originates from post-thymic mature T lymphocytes (5), and both are typically associated with a complex tumor microenvironment. The simultaneous or sequential occurrence of HL and NHL in the same patient is rare (9,10), and the association between such discordant lymphomas and immune system disorders or HL treatment remains unclear. The present study describes the case of a patient who was initially diagnosed with nodular sclerosing-type CHL, which later evolved into peripheral

T-cell lymphoma, not otherwise specified (PTCL-NOS), after 3 years. The clinicopathological features and potential mechanisms underlying this transformation were further explored through a review of the literature.

Case report

A 73-year-old man was diagnosed with CHL at Yantai Yuhuangding Hospital (Yantai, China) in December 2012. Fresh ~4-cm lymph node specimens were obtained by surgical resection from the left neck, and were homogenized and suspended in RPMI medium (Gibco; Thermo Fisher Scientific, Inc.) for flow cytometry. Histological examination revealed features indicative of nodular sclerosing-type CHL. After obtaining appropriate written informed consent, including an explanation of the risks and benefits, left posterior iliac crest bone marrow aspiration and biopsy were performed. Flow cytometry revealed no monotypic population and CD25-positive cells within normal limits (data not shown). A complete blood count performed in December 2012 showed unremarkable white blood cell morphology and an elevated eosinophil count of 31% (normal count, 0.4-8%), but with no immature eosinophils. Red blood cell indices were essentially normal, with minimal anisocytosis and poikilocytosis, while platelets exhibited normal granularity. The left cervical lymph node was excised, and complete destruction of the lymph node structure was revealed under low magnification in a light microscope field (Olympus BX53M; Olympus Corporation). The fibrotic lymph node capsule divided the lymph node into nodules of varying sizes (Fig. 1A). Large mononuclear cells, occasionally binucleated or multinucleated, with prominent nuclei and nucleoli were observed amidst numerous neutrophils, eosinophils and lymphocytes within the nodules (Fig. 1B).

For immunohistochemistry, the specimen was fixed in 10% neutral formalin for 12 h at room temperature, embedded in paraffin and sectioned into 4-μm continuous slices. Immunohistochemical staining was performed using the BenchMark ULTRA immunohistochemistry staining system (Roche Diagnostics). The specific steps are as follows: i) Paraffin-embedded sections were dewaxed and hydrated at 72˚C, followed by rinsing with PBS for 4 min; ii) according to the requirements of the primary antibodies (Table I), antigen retrieval was performed at 95˚C for 30 min; iii) sections were rinsed with PBS, and then incubated with an endogenous peroxidase inhibitor (3% H_2O_2) at 37˚C for 4 min; iv) sections were rinsed again with PBS and then incubated with primary antibodies at 37˚C for 32 min; v) the peroxidase-conjugated secondary antibody (Table I; 1:20) was added to the sections at 37˚C for 8 min; vi) freshly prepared DAB color development reagent was added to the sections at 37˚C for 8 min to visualize staining; vii) sections were rinsed with running water to terminate the color development and were counterstained with hematoxylin for 8 min at 37˚C; viii) the blue color was restored with PBS for 8 min, and the sections were dehydrated with gradient ethanol, cleared with xylene and sealed with neutral balsam. Known positive tissue (normal lymph nodes from the same patient) was used as a positive control and PBS was used instead of the primary antibody as a negative control. The stained sections were scanned using a 3D Pannoramic SCAN

Table I. Antibody details.

Antibody	Clone no.	Cat. no.
Primary antibodies		
CD1a	EP80	ZA-0544
CD2	UMAB6	ZM-0278
CD3	EP41	ZA-0503
CD4	EP204	ZA-0519
CD5	EP77	ZA-0510
CD8	SP16	ZA-0508
CD10	UMAB235	ZM-0283
CD15	MMA+BY87	ZM-0037
CD20	L26	ZM-0039
CD21	EP64	ZA-0525
CD23	EP75	ZA-0516
CD30	EP154	ZA-0591
CD45	2B11&PD7/26	ZM-0183
CD57	NK1	ZM-0058
CD68	PG-M1	ZM-0464
Bcl2	EP36	ZA-0536
Bcl6	OTIR1D9	ZA-0583
EMA	GP14	ZM-0095
EBER	CS1-4	ZM-0105
Igκ	CH15	ZM-0160
Igλ	SHL53	ZA-0544
IgD	/	ZA-0443
PAX5	EP156	ZA-0566
Pd1	UMAB199	ZM-0381
TdT	EP285	ZA-0625
Secondary antibodies		
Goat Anti-Rabbit	/	A0545
Goat Anti-Mouse	/	A4416

The primary antibodies were purchased from OriGene Technologies, Inc., and the secondary antibodies were purchased from Sigma-Aldrich; Merck KGaA. Ig, immunoglobulin; EMA, epithelial membrane antigen; EBER, Epstein-Barr virus-encoded RNA; TdT, terminal deoxyribonucleotidyl transferase.

digital slide scanner [Bio-One Scientific Instrument (Beijing) Co., Ltd.]. Immunohistochemical staining demonstrated positivity for PAX5 (Fig. 1C), and negativity for CD20 (Fig. 1D), CD10, immunoglobulin (Ig)κ and λ chains, and IgD on the surface of B cells (data not shown). T cells were negative for CD3 (Fig. 1E), PD1 and CD57 (data not shown), whereas other cells were positive for CD30 (Fig. 1F), CD15 and Bcl-6, and negative for Bcl-2 and epithelial membrane antigen (data not shown). CD21 and CD23 staining highlighted the follicular dendritic cell meshwork (data not shown), while Epstein-Barr virus (EBV)-encoded small RNA (EBER) staining was negative, as determined by *in situ* hybridization (11) (data not shown). In January 2013, the patient received four cycles of doxorubicin, bleomycin, vinblastine and dacarbazine chemotherapy (ABVD regimen; doxorubicin 25 mg/m², on the 1st and 15th day; bleomycin 10 mg/m², on the 1st and 15th day;
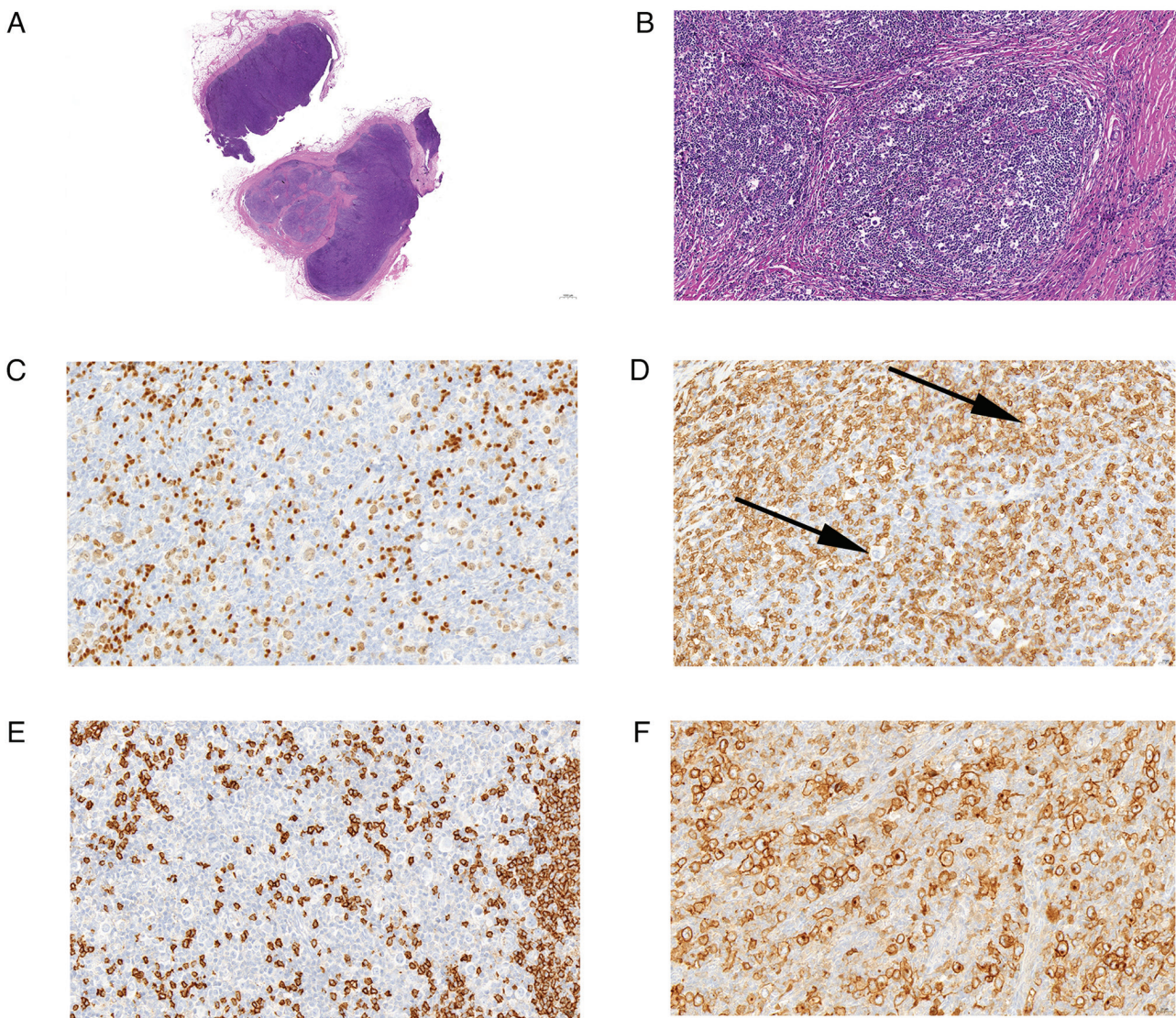
Figure 1. H&E and partial immunohistochemical analysis were used to diagnose classical Hodgkin lymphoma (nodular sclerosis type). (A) Under low power, the lymph node capsule was fibrotic and divided by the thick fiber bundle into nodules of different sizes (H&E; magnification, x9). (B) Large cells were mainly mononuclear, occasionally binucleated or multinucleated, with large nuclei and nucleoli (H&E; magnification, x200). Immunohistochemically, the cell surface of B cells was (C) positive for PAX5 (magnification, x194) and (D) negative for CD20 (black arrows indicate the negative cells; magnification, x400). Cell surface of other cells was (E) negative for CD3 and (F) positive for CD30 (magnification, x400). H&E, hematoxylin and eosin.

vincristine 6 mg/m^2, on the 1st and 15th day; dacarbazine 375 mg/m^2, on the 1st and 15th day; each cycle is 28 days), resulting in complete remission.

A total of 3 years later, the patient presented with enlarged lymph nodes in the left groin. A fresh left groin lymph node specimen, obtained in October 2015, consisted of a ~2.0x1.5x1.0 cm lymph node, with an attached ellipse of healthy-looking skin and benign adipose tissue measuring 2.5x1.0 cm. The patient underwent a karyotype test in October 2015, exhibiting a karyotype of 46, XY. Histological examination using a light microscope revealed a disrupted lymph node structure with features suggestive of dermatopathic lymphadenitis with nodular T-zone hyperplasia under low-power magnification (Fig. 2A) and small atypical T cells amidst abundant blood vessels under high-power magnification (Fig. 2B). Immunohistochemical staining identified notable CD3 expression (Fig. 2C) and a partial CD8 T-cell population (data not shown). Immunohistochemically, the

Ki67 proliferation rate was ~98% (Fig. 2D). Consistent with a diagnosis of PTCL, strong clonal T-cell receptor (TCR)-γ (*TRG*) gene rearrangement was detected by molecular analysis (PCR) (12) (Fig. 2E) and flow cytometry (Fig. 3A-C) with increased proliferation. Minimal superficial perivascular lymphocytic inflammation with scattered eosinophils was observed in the skin section (data not shown), and no evident T-cell lymphoma was identified. Immunohistochemical staining of B cells revealed negativity for CD20 and PAX5, and positivity for CD2, CD3, CD5 and CD8, while T cells were negative for CD4 and PD1, and other cell types were negative for CD45, CD30, CD15, CD1a, CD68, terminal deoxyribonucleotidyl transferase and EBER. Peripheral blood and bone marrow aspirates, and a biopsy from the iliac crest exhibited hypercellular bone marrow (60% cellularity) with panhyperplasia, including ~20% eosinophils in both peripheral blood and bone marrow (Fig. 2F). The marrow had an estimated myeloid:erythroid ratio of
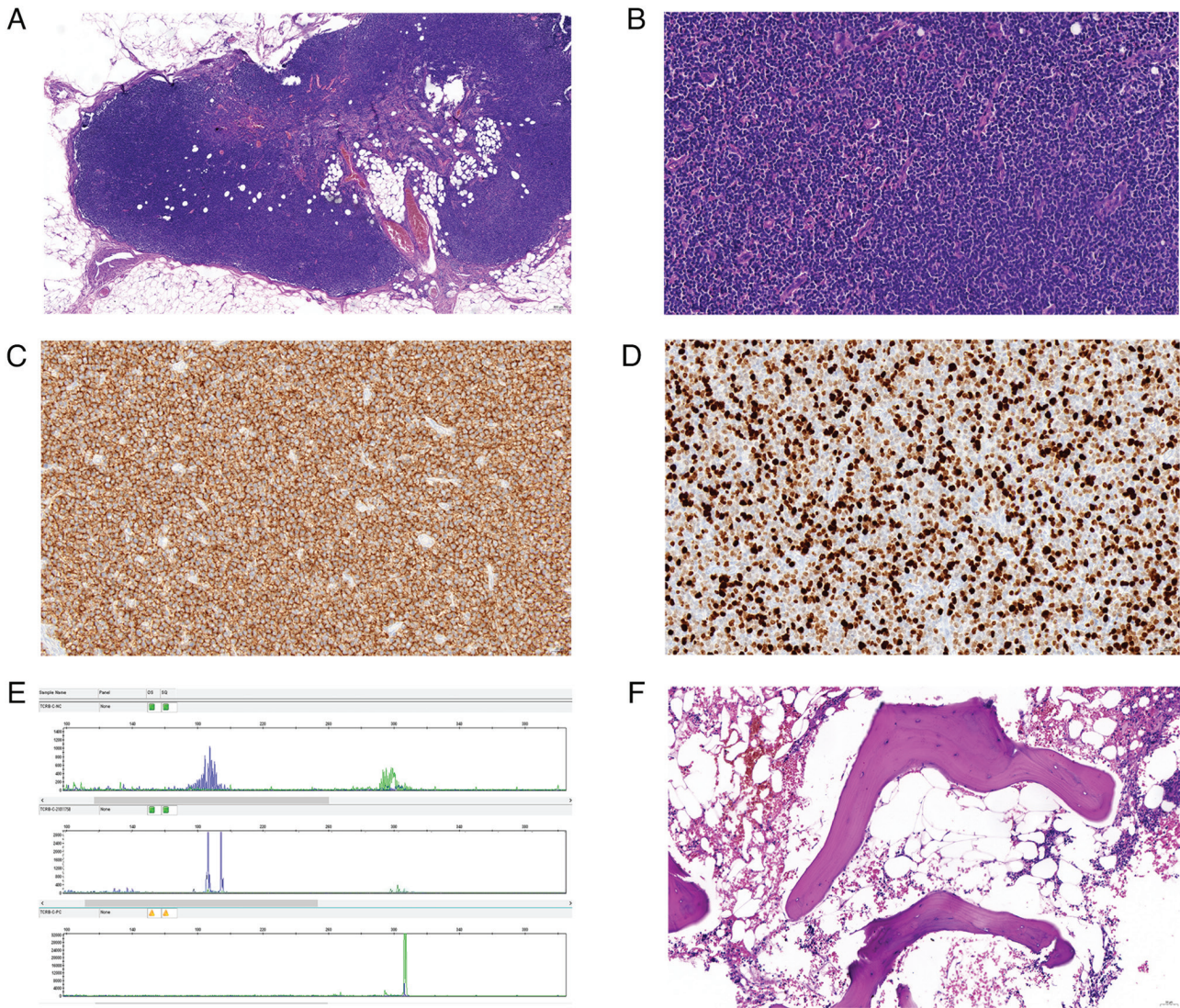
Figure 2. H&E, partial immunohistochemistry and T-cell receptor-γ rearrangement analysis for the diagnosis of peripheral T-cell lymphoma. (A) Under low power, no lymphoid aggregates were identified in T-cell immunostaining (H&E; magnification, x47). (B) Under high power, dermatopathic lymphadenitis with nodular T-zone hyperplasia of small atypical T cells, histiocytes, Langerhans cells and dendritic cells was detectde (H&E; magnification, x400). Immunohistochemistry showed (C) positive CD3 staining (magnification, x400); (D) a Ki67 proliferation rate of ~98% Ki67 (magnification, x400). (E) Molecular study (PCR) showed strong clonal T-cell receptor-γ gene rearrangement. (F) Bone marrow biopsy was hypercellular (60%) with an estimated myeloid:erythroid ratio of 4:1 (magnification, x200). H&E, hematoxylin and eosin.

4:1, with no lymphoid aggregates. Flow cytometry (13) was positive for T-cell lymphoma, and the significance of the positive *TCR* gene rearrangement was unclear in the context of a normal complete blood count and the absence of morphologic lymphoid aggregates. The molecular findings may have reflected differences in sampling or may have been positive due to the presence of some clonal cells in the peripheral blood. No HL was detected. The patient subsequently received six cycles of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP regimen; cyclophosphamide 75 mg/m^2, intravenous injection, on the 1st day; doxorubicin 50 mg/m^2; vincristine 1.4 mg/m^2, up to a maximum of 2 mg, intravenous bolus injection, on the 1st day; prednisone 60 mg/m^2, oral administration, from the 1st to 5th day; 21 days per cycle) but was lost to follow-up in October 2022, having achieved complete remission prior to this time.

Discussion

CHL is typically classified as a germinal center B-cell neoplasm (4), with T-cell lineage accounting for <5% of all cases (14). This observation is consistent with the updated World Health Organization classification of hematolymphoid neoplasms in 2017 (13-17). In addition, T-cell NHL is uncommon, constituting only 7-12% of all NHL cases (10,18). The co-occurrence of NHL and HL is rare, particularly when the NHL component originates from the T-cell lineage (19-21). Various explanations have been proposed to account for the development of HL followed by T-cell lymphoma, including therapy-induced effects, immunodeficiency-related factors and tumor biological interactions (7,22,23).

A search of the PubMed (https://pubmed.ncbi.nlm.nih.gov/) database identified 10 cases, including the present case, in which CHL transformed into PTCL-NOS following
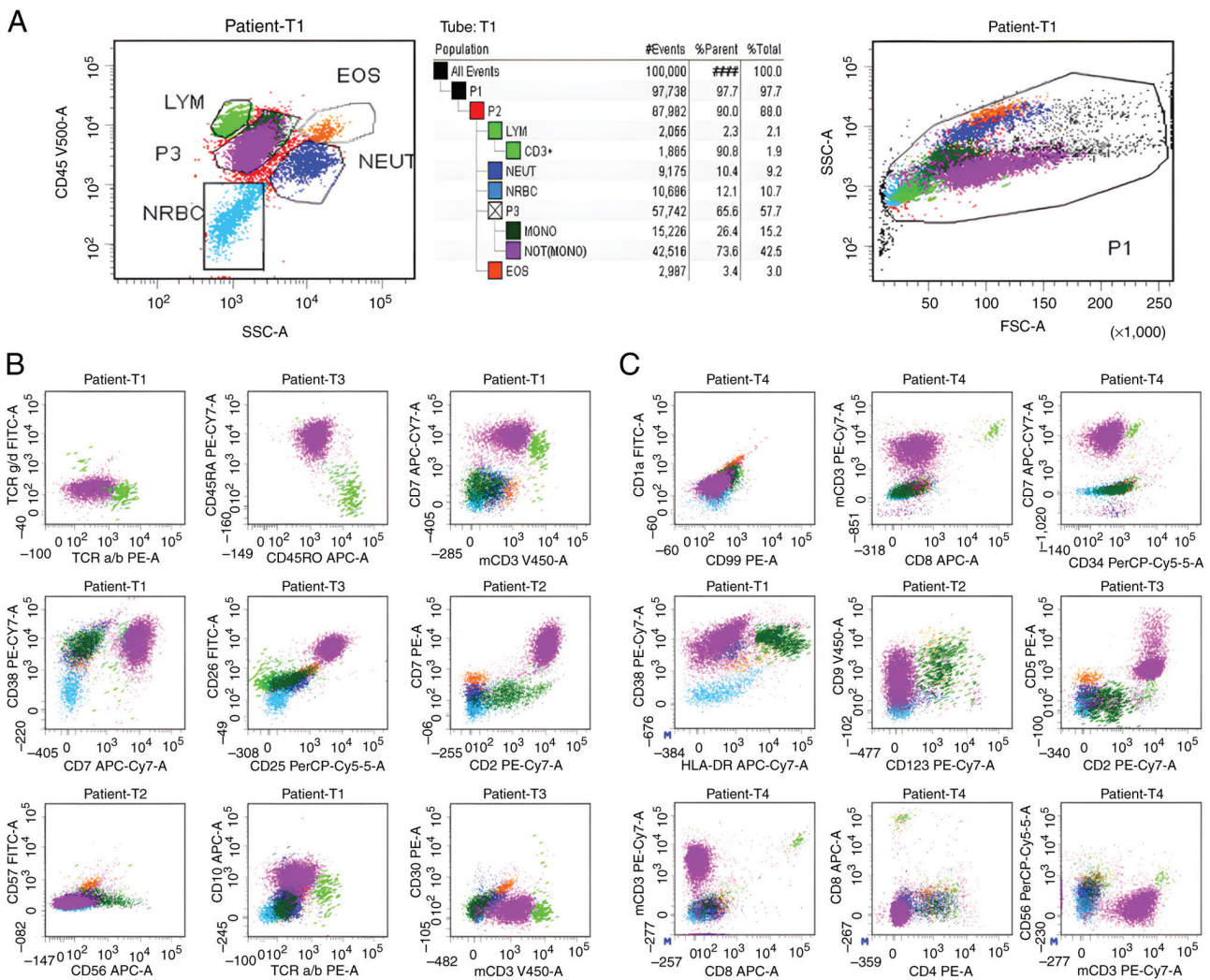
Figure 3. (A-C) Bone marrow aspiration biopsy diagnosis was peripheral T-cell lymphoma. (A) In the bone marrow sample, abnormal expression of T-cell antigens was observed, with abnormal T cells accounting for 42.5% of nucleated cells. (B) In the CD45/SSC primitive cell region, a cluster of abnormal cells with a larger FSC (red) was detected, which expressed CD7, CD2, CD45RA, CD38, CD25 and CD26, and weakly expressed CD10 and mCD3. (C) Part of the aforementioned red cell cluster expressed CD9, weakly expressed CD5, lacked expression of CD4, CD8 and the primitive cell marker CD34. In general, the cells in this cluster expressed TCRab (dim), CD25, CD26, mCD3 (dim), CD7str/+, CD5dim/+, CD45RA, CD2, CD38; and did not express CD57, CD8, CD45RO, CD16, CD56, TCRgd, CD4, CD30, CD10, CD99, CD1a, CD34, HLA-DR. FSC, forward scatter; dim, diminished; str, strong.

treatment. A summary of the clinicopathological features of these cases is provided in Table II. The male-to-female ratio was 9:2 (males 81.82%) and the ages ranged between 18 and 76 years (mean age, 64 years), with most patients being middle-aged or elderly (>45 years old; 9/11; 81.82%), although a few patients were younger. The clinical presentations varied among cases but lymph node enlargement and weight loss were commonly reported. Most biopsies used for CHL diagnosis were obtained from enlarged lymph nodes. Regarding CHL staging, cases 2 (7), 5 (24), 6 (25), 7 (26) and 8 (27) (Table II) were specifically staged, but staging of the other cases was unclear and was inferred from available data. Most diagnoses occurred at an advanced stage.

Regarding EBV infection, except for case 5 (18) in whom the association was not clearly indicated, cases 1 (26), 2 (7), 8 (27) and 9 (28) were reported to be EBV-positive at the initial diagnosis of CHL, whereas cases 3 (9), 4 (29), 6 (25), 7 (26) and the current case were EBV-negative. In terms of the mechanism underlying transformation, Huettl *et al* (26)

reported the case of two patients in whom lymphoma transformation was suggested to be related to T-cell clonality, whereas Nakazaki *et al* (9) reported one patient in whom lymphoma transformation could be associated with the interleukin (IL)-13 and IL-4 pathways. Additionally, lymphoma transformation might have been related to immunodeficiency in cases 4 (29), 5 (24), 6 (25) and the current case, while there was a possible association with chemotherapy in cases 4 (29), 6 (25), 9 (28) and the present case, and a potential link to EBV infection in cases 8 (27) and 10 (30). Some researchers (30) have suggested EBV infection as a possible factor in the early onset of T-cell lymphoma, whereas others (9) have proposed different mechanisms. Nakazaki *et al* (9) reported a case of HL in a patient treated with dupilumab for 1 year, who was diagnosed with a rare combination of discordant HL and PTCL. This previous study emphasized the need for vigilance regarding the potential development of lymphoma associated with the IL-13 and IL-4 pathways in patients with unresponsive atopic dermatitis treated with dupilumab, and suggested the need to consider

Table II. Clinical data of patients with CHL transformed into PTCL after treatment.

First author, year	Case no./Age, years/Sex	Clinical presentation	Biopsy site for CHL diagnosis	CHL subtype	CHL stage	EBV infection	Treatment for CHL	Time from diagnosis of CHL to PTCL-NOS	Biopsy site for PTCL-NOS diagnosis	Treatment for PTCL-NOS	Prognosis	Mechanisms of transformation	(Refs.)
Huettl, 2019	1/18/M	Enlarged retroperitoneal LNs, splenomegaly, multiple bone lesions and B-symptoms	Bone marrow trephine specimen	NA	NA	EBER$^+$	6BEACOPP escalated	28 months	Liver biopsy	NA	D	T-cell clonality	(26)
Brown, 2004	2/32/M	Cervical lymphadenopathy, prolonged bronchitis	Right posterior cervical LN	NA	IIIA	EBER$^+$	6ABVD	2 years	Left submandibular lymphadenopathy	Salvage chemotherapy followed by autologous stem cell transplantation	NA	Immunodeficiency	(7)
Nakazaki, 2022	3/47/M	Scaly erythematous patches on the upper and lower limbs with marked pigmentation, extensive squamous erythema and obvious pigmentation of the right armpit	Right axillary LN	NS	NA	EBV- LMP-1$^-$	6AAVD	2 years	Left thigh	NA	NA	Blocking of IL-13 and IL-4 pathways	(9)
Mohrmann, 2000	4/47/M	Right axillary LN enlargement, mild fatigue, weight loss and flu-like symptom	Right axillary LN	NS	NA	EBV- LMP-1$^-$	6ABVD	5 years	Posterior cervical LN	NA	Remission	Immunodeficiency, chemotherapy	(29)

Table II. Continued.

First author, year	Case no./Age, years/Sex	Clinical presentation	Biopsy site for CHL diagnosis	CHL subtype	CHL stage	EBV infection	Treatment for CHL	Time from diagnosis of CHL to PTCL-NOS	Biopsy site for PTCL-NOS diagnosis	Treatment for PTCL-NOS	Prognosis	Mechanisms of transformation	(Refs.)
Włodarska, 1993	5/54/M	Weight loss, fever and symptoms of arthritis	Cervical LN	NS	IIIA	NA	8MOPP/ABVD	2 years	Cervical LN	NA	NA	Immunodeficiency	(24)
Chang, 2015	6/64/F	Abrupt weight loss, abdominal pain and bloating	Left supraclavicular LN	NS	IIIB, or possibly stage IV/BE	EBER⁻	3ABVD	2 years	Right inguinal LN	3 cycles etoposide-containing regimen	D	Immunodef iciency	(25)
Huettl, 2019	7/65/M	Enlargement of LNs in left armpit and neck, weight loss	Cervical LN	NS	IB	EBER⁻	4ABVD, 30 Gy radiotherapy	10 months	Left-sided inguinal lymphadenopathy and urosepsis	Antibiotics	NA	T-cell clonality	(26)
Niedobitek, 2000	8/65/M	Weight loss, fever and general malaise	Left axillary LN	NS	IVB	EBER⁺	COPP/ABVD	4 years	Cervical LN	CEVD	D	EBV infection	(27)
Zhu, 2016	9/72/M	Weight loss, poor mental health, emaciation, occasional fever	Cervical LN	MC	NA	EBER⁺	6ABVD	3 years	Cervical LN	NA	D	Chemotherapy	(28)
Oka, 2000	10/76/F	A palm sized, ill-defined and elastic hard tumor on the right forearm and multiple	Submandibular LN	NA	NA	EBER⁺	ABVD	9 years	Skin tumor	CHOP	D	EBV infection	(30)

Table II. Continued.

First author, year	Case no./ Age, years/ Sex	Clinical presentation	Biopsy site for CHL diagnosis	CHL subtype	CHL stage	EBV infection	Treatment for CHL	Time from diagnosis of CHL to PTCL-NOS	Biopsy site for PTCL-NOS diagnosis	Treatment for PTCL-NOS	Prognosis	Mechanisms of transformation	(Refs.)
		subcutaneous tumors on the back; B symptoms, including fever and general signs											
Song, 2024	Present case/73	LN enlargement	Left cervical LN	NS	NA	EBER⁻	4ABVD	3 years	Left inguinal LN	CHOP	NA	Chemotherapy and immunodeficiency	NA

LN, lymph node; CHL, classical Hodgkin lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine and dacarbazine; AAVD, brentuximab vedotin (Adcetris), vinblastine and dacarbazine; CEVD, cyclophosphamide, etoposide, vindesine and dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine (Oncovin) and prednisone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; COPP, cyclophosphamide, vincristine, methylbenzylhydrazine and prednisone; MOPP, mechlorethamine, vincristine, procarbazine and prednisone; CR, complete remission; EBER, Epstein-Barr virus-encoded RNA; EBV-LMP-1, Epstein-Barr virus latent membrane protein; NS, nodular sclerosis type; MC, mixed cellularity; NA, not available; F, female; M, male; D, died.

the possibility of complex or discordant lymphomas in the diagnosis and treatment of lymphoma (9). Other researchers have argued that most cases of PTCL following treatment for HL could result from therapy-induced immunodeficiency, rather than from clonal progression (7). Clonal rearrangement of *TCR* genes, as an accepted diagnostic feature of T-cell lymphoma, was observed in most cases according to a previous study (31). There have also been reports of Ig heavy-chain gene rearrangements in Reed-Sternberg cells (31,32), but further studies are needed to clarify this phenomenon. A previous study (31) proposed that *TCR* and *IGH* clonal rearrangements indicated that the tumor cells were not clonally related, but may occur simultaneously and inhabit the same immune microenvironment. Brown *et al* (7) described four patients with composite lymphomas, one of whom showed *TCR* rearrangement in Reed-Sternberg cells, raising the possibility that HL may evolve from basal T-cell NHL. The present study describes the case of an elderly male patient who developed PTCL-NOS 3 years after chemotherapy for an initial diagnosis of nodular-sclerosing CHL. Mohrmann and Arber (29) reported a similar case of composite lymphoma at presentation, although their patient was diagnosed with PTCL-NOS after 2 years of intermittent chemotherapy; however, the existence of composite lymphoma at the time of CHL diagnosis remains uncertain, because only a cervical lymph node was obtained and confirmed as HL. The occurrence of PTCL-NOS in this previously described case may thus be related to chemotherapy.

Following diagnosis, nine patients, including the current patient, underwent ABVD chemotherapy, whereas case 1 (26) received bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP regimen) and radiotherapy, respectively, but all progressed to PTCL-NOS at varying intervals, with the longest duration being 9 years in case 10 (30) and the shortest being 10 months in case 7 (26). Regarding the treatment plans for patients diagnosed with PTCL-NOS, the treatment regimen was not specified in cases 1 (26), 3 (9), 4 (29) and 5 (24), while the other patients received different treatment modalities. Brown *et al* (7) reported on one patient (case 2) who underwent autologous stem cell transplantation post-chemotherapy, whereas Chang *et al* (25) documented a patient (case 6) who was treated with an etoposide regimen for three cycles. Huettl *et al* (26) reported a patient (case 7) who was treated with antibiotic therapy, and Niedobitek *et al* (27) reported on one patient (case 8) treated with cyclophosphamide, etoposide, vindesine and dexamethasone (CEVD regimen). Additionally, Zhu *et al* (28) reported on a patient (case 9) who did not receive any treatment, whereas Oka *et al* (30) reported on a patient (case 10) who was treated with the CHOP regimen. Concerning the prognosis, cases 2 (7), 3 (9), 5 (24) and 7 (26) had unspecified outcomes. The current patient and case 4 (29) achieved remission after treatment; however, the remaining patients succumbed during follow-up. Notably, all CHL subtypes presented with nodular sclerosis, except for cases with unspecified subtypes [cases 1 (26), 2 (7), 10 (30)] and one patient [case 9 (28)] with mixed-cell type. Cases 3 (9), 4 (29), 5 (24), 7 (26), 8 (27), 9 (28) and the present case predominantly involved middle-aged and elderly men initially diagnosed with CHL that subsequently transformed into PTCL-NOS post-treatment. Cases 6 (25) and 10 (30)

involved elderly women, while one patient (case 10) (30) was initially diagnosed with mixed-cell type of HL, which transformed into PTCL-NOS after treatment. These cases suggest that increased attention should be paid to the treatment of middle-aged and elderly patients with nodular sclerosing-type CHL in clinical practice, given the higher likelihood of transformation into PTCL-NOS post-treatment in these patients. Once PTCL-NOS develops, the prognosis is typically poor. No apparent immunodeficiency was noted in the patient described in the present study prior to CHL diagnosis, suggesting that PTCL-NOS may have been primarily caused by the chemotherapy. The transformation of CHL into PTCL-NOS post-treatment is rare, but the mechanism underlying this transformation may be associated with the complex tumor microenvironment of CHL. Although the present study conducted a retrospective review of the relevant literature, the lack of practical clinical data and experience may have led to different conclusions, recommendations and actual situations, representing a significant limitation of this study. The precise mechanisms thus remain unclear. Notably, a full understanding of rare and/or complex diseases often requires the accumulation of data over a long period of time, and despite the thorough exploration of existing research materials, the scarcity of cases means that some pathophysiological processes may have been missed. The conclusions are also limited by the lack of detailed analysis of different patient groups. Rare or complex diseases may manifest differently and have distinct mechanisms in diverse populations, influenced by factors such as age, sex, genetic background and lifestyle; however, these factors were not fully considered because of constraints in terms of research resources and time, potentially leading to a less understanding of specific patient groups.

In conclusion, the transformation from CHL to PTCL-NOS following treatment is rare, with a predilection towards men. Nodular sclerosing-type CHL is the predominant subtype prone to transformation into PTCL-NOS. Patients undergoing this transformation typically exhibit a poor prognosis, with potential mechanisms linked to the intricate tumor microenvironment characteristic of CHL. Future research should thus place greater emphasis on integration with clinical practice, to collect and analyze clinical data to validate and refine the theoretical models. In summary, although this case report and literature review may improve understanding of the relevant mechanisms underlying the transformation to PTCL-NOS following treatment for CHL, there remain a number of limitations and challenges. Further research and analysis are needed to clarify the relevant mechanisms and provide stronger support for the accurate diagnosis and effective treatment of patients.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LS, YaY and GY designed the project. LS wrote the draft, and WW, NZ and GY revised the manuscript. NZ, YP and LS completed the revision of the article, including image modification, data management, data analysis and figure generation. WW performed flow cytometry. YiY, JW and YG prepared the figures, collected data and prepared tissue slides. SW and YW collected the literature and analyzed the data. PY and XS performed the molecular test and pathological diagnosis. GY and YaY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Based on the ethical rules for biomedical research related to humans issued by the national health and family planning commission, and The Declaration of Helsinki, the Ethical Review Board discussed the study protocol and informed consent, and voted anonymously on June 21, 2020. The Institutional Ethical Review Board decided that the main participants qualified for clinical study, the study design was eligible, practical and scientific, and the rights and interests of the patients were fully protected. The present study was approved by the Institutional Ethical Review Board of Yantai Yuhuangding Hospital (approval no. [2020-43]) and this was valid for 1 year from the date of approval.

Patient consent for publication

Written informed consent was obtained from the patient prior to the enrollment into this case report.

Competing interests

The authors declare that they have no competing interests.

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