Case report

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Classical Hodgkin lymphoma following follicular lymphoma: a case report

Bomi Kim

Department of Pathology, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

The simultaneous, composite, or sequential occurrence of follicular lymphoma (FL) and classical Hodgkin lymphoma (HL), both of which originate from germinal center B-cell, is rare. Questions have been raised with regard to the type of tests that pathologists should perform when observing the presence of a "large-cell lymphoma" following an FL and what are the most critical pathological points for diagnosis. Here, we present a case of a classical HL following an FL after administering rituximab-bendamustine (R-Benda) chemotherapy. Furthermore, we also summarized the literature and compared this case with other HLs that followed FLs. A 55-year-old woman was diagnosed with a grade 3A FL of the breast and axillary lymph node masses. She completed six R-Benda chemotherapy cycles for stage IV FL. Twenty-three months after the diagnosis, follow-up image studies showed an increase in the size and number of the lesions. Biopsies of the neck lymph node and liver were performed, and the diagnosis was classical HL. Sequential or composite FL and HL may sometimes develop from the same clone because they share the same genetic alterations, such as B-cell lymphoma (Bcl)-2 or Bcl-6 translocation. When a large-cell lymphoma is found after the treatment of FL, classical HL should be considered a pathological differential diagnosis, and histological, immunohistochemical, or molecular investigations must be considered during the diagnostic process.

Keywords: Follicular lymphomas; Hodgkin disease; Immunoglobulin heavy chain genes; Proto-oncogene protein c-bcl-2

Introduction

Clinicians and pathologists often encounter secondary tumors after the treatment of primary tumors. In malignant lymphomas, it is well known that low-grade lymphomas such as follicular lymphomas (FLs) can be transformed into high-grade, diffuse large B-cell lymphomas (DLBCLs) [1]. Although Hodgkin lymphoma (HL) and non-HL are different types of malignant lymphoma, reports on "consequent" lymphomas are rare [2]. These tumors, often found in breast or prostate cancers, should be differentiated from lymphomas that changed their morphological findings due to the administration of treatment. Thus, which tests should pathologists perform when observing the presence of a "large-cell lymphoma" following a FL? What are the most critical pathological points for diagnosis? Here, we present a case of a classical HL that developed following rituximab-bendamustine (R-Benda) chemotherapy for FL treatment. We also summarized the literature and compared this case with other HLs that followed FLs.

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Corresponding author: Bomi Kim, MD, PhD
Department of Pathology, Inje University Haeundae Paik Hospital, Inje University College of Medicine, 875 Haeun-daero, Haeundae-gu, Busan 48108, Korea
Tel: +82-51-797-3112 • Fax: +82-51-797-3101 • E-mail: domabem96@paik.ac.kr

Case

Ethical statements: This study followed the recommendations of the World Medical Association Declaration of Helsinki and was approved by Institutional Review Board (IRB) of Inje University Haeundae Paik Hospital in Busan, Korea (IRB No: 2021-01-009). The need for informed consent was waived due to the retrospective nature of the study.

A 55-year-old Asian woman presented with a painful mass on the left anterior chest wall. She was being treated for hypertension, hyperlipidemia, diabetes mellitus, and rheumatoid arthritis. Chest computed tomography (CT) revealed multiple subcutaneous enhancing masses on the left breast, right lower back, and mid-back, measuring between 12 and 26 mm (Fig. 1A–1C). The axillary lymph nodes on the left side were enlarged (Fig. 1B, 1C). The neck CT was normal (Fig. 1D). Excisional biopsies of the left breast and the solid axillary masses were performed.

A low-power view of the breast lesion showed an abnormal follicular growth pattern, which did not have tingible body macrophages or well-developed mantle zones (Fig. 2A). The abnormal follicular pattern was also found in the extranodal lymphoid adipose tissue through lymphoid capsules (Fig. 2B), with neoplastic follicles composed of centroblasts (Fig. 2C). However, Reed-Sternberg, Hodgkin cells, or popcorn cells were absent. The CD21 immunohistochemistry highlighted follicular dendritic cell meshworks, including an abnormal structure of the adipose tissue (Fig. 2D). The CD20 (Fig 2E) and B-cell lymphoma (Bcl)-6 antibodies (Fig. 2F) reacted to the neoplastic follicles. Sparse CD10-positive cells were observed in neoplastic follicles (Fig 2G). Moreover, the Bcl-2 immunohistochemistry showed a variable extent of positivity in neoplastic follicles (Fig. 2H), and some follicles were positive for Bcl-2 immunohistochemistry, with a diffuse or weakly patchy pattern (Fig. 2H). The expression of CD10, CD5, MUM1, and cyclin D1 was negative, and CD3-positive intrafollicular T cells were also found in neoplastic follicles. The Ki-67 labeling index was as high as 50% (Fig. 2I). Thus, the histological findings of the axillary

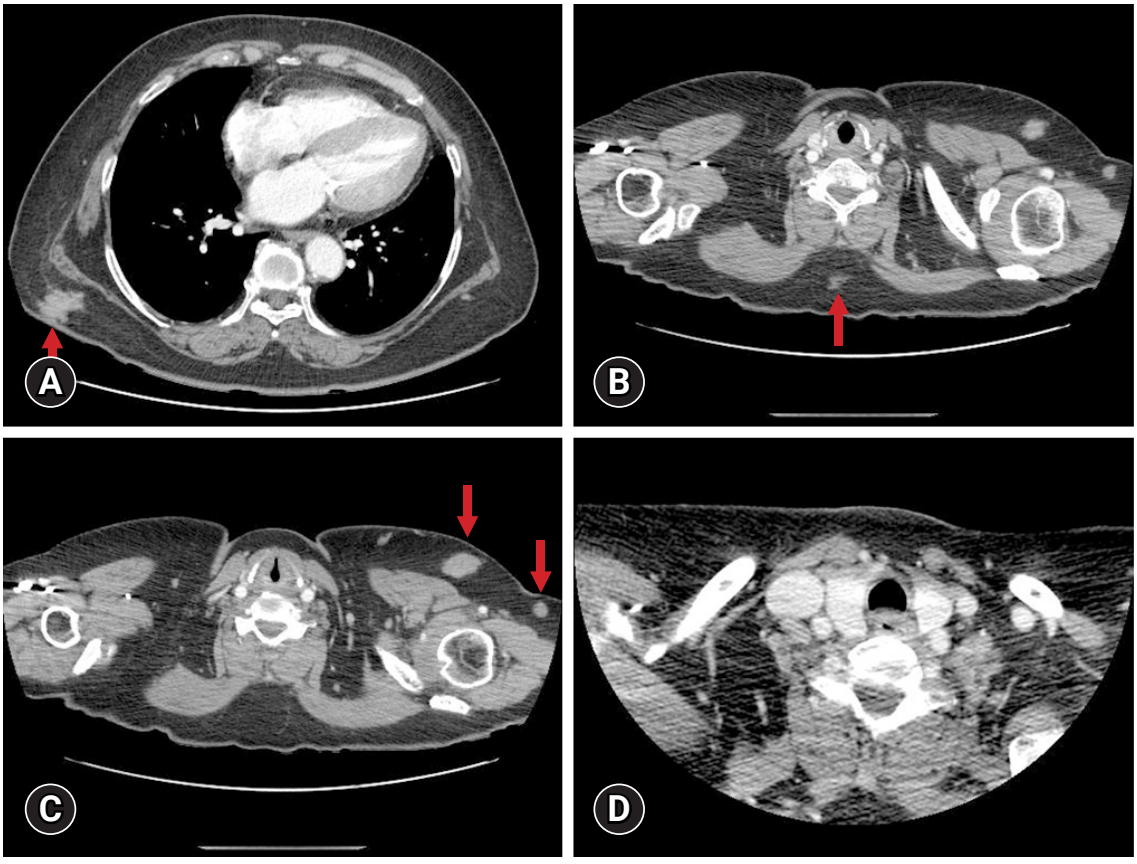

Fig. 1. Chest computed tomography (CT) images display multiple subcutaneous enhanced masses (arrows) measuring (A) 29 mm at the right lower back, (B) 17 mm at the mid-back, and (C) 12 mm at the left breast. (D) No abnormal findings are observed in the neck CT.

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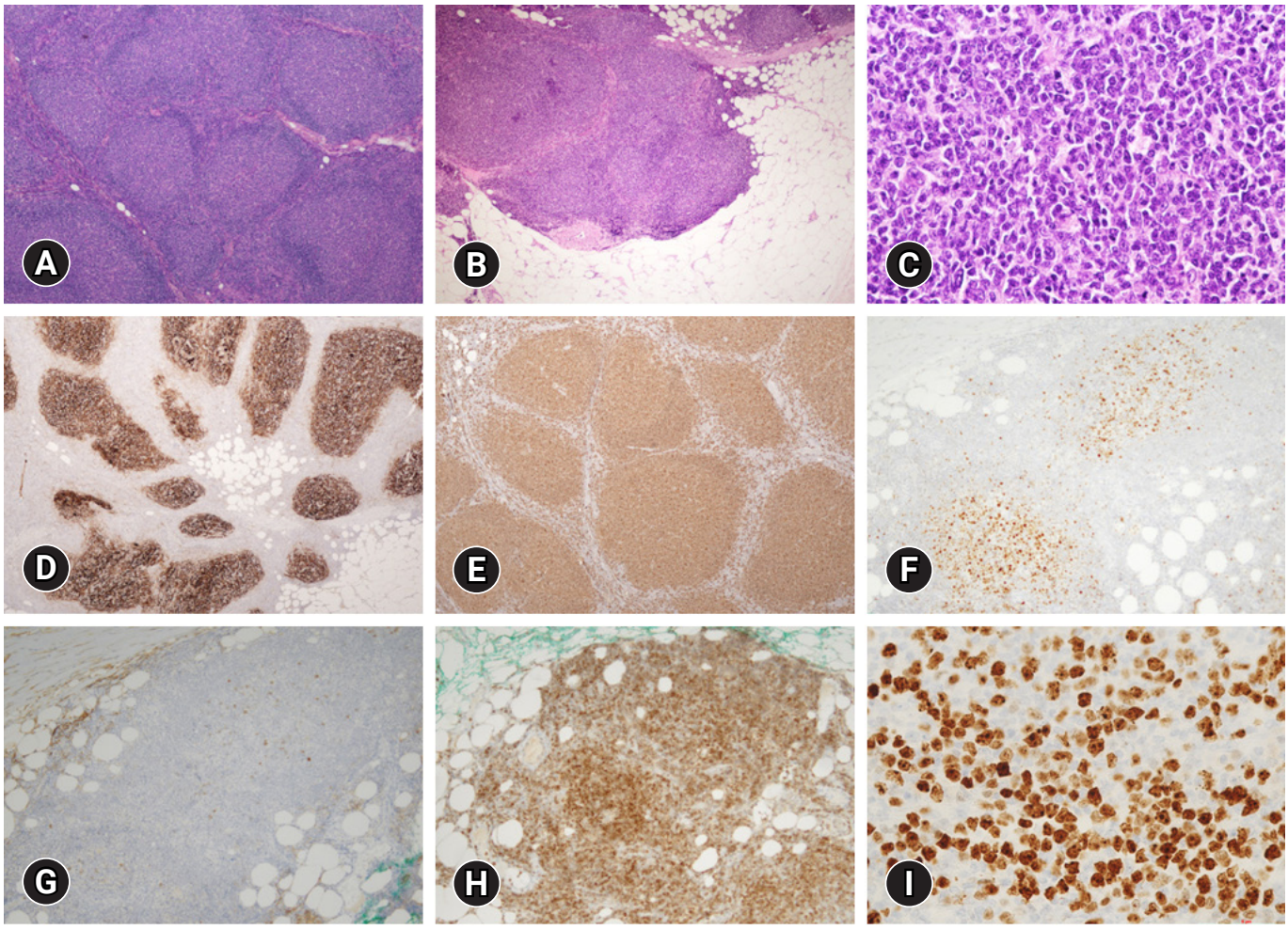

Fig. 2. Microscopic findings of the left breast. (A) Low-power magnification revealing a proliferation of neoplastic follicles with slight size variation and attenuated mantle zone (hematoxylin and eosin [H&E] stain, ×40). (B) Abnormal follicular growth patterns extending to the fatty tissue outside the lymph node through the lymph node capsule (H&E stain, ×40). (C) Neoplastic follicles predominantly composed of centroblasts, consistent with follicular lymphoma, grade 3A. Tingible body macrophages are absent (H&E stain, ×400). (D) CD21 immunohistochemistry highlighting follicular dendritic cell meshworks inside and outside the lymph node (CD21 immunohistochemistry, ×40). (E) Anti-CD20 (CD20 immunohistochemistry, ×40) and (F) anti-Bcl-6 antibodies reacting to tumor cells (Bcl-6 immunohistochemistry, ×100). (G) Sparse CD10-positive cells observed in neoplastic follicles (CD10 immunohistochemistry, ×100). (H) Bcl-2 expression in neoplastic follicles (Bcl-2 immunohistochemistry, ×100). (I) The Ki67 labeling index with 50% of tumor cells ratio (Ki-67 immunohistochemistry, ×400).

masses were identical to those of the breast. The diagnosis was FL, grade 3A, with a follicular pattern.

The positron emission tomography (PET) for staging workup revealed multiple subcutaneous nodules of the shoulder, back, flank, breast, and axilla and enlarged lymph nodes of the left axilla, anterior diaphragmatic, and right interlobar areas (Fig. 3A). The bone marrow test was negative for malignant lymphoma. Although chemotherapy was recommended for stage IV FL, the patient refused it and visited a clinic for regular radiological studies. After 17 months of FL, the PET revealed new lesions of the supraclavicular, mediastinal, and left axillary lymph nodes and increased size of the anterior diaphragmatic lesions, despite no evidence of progression in previous image tests (Fig. 3B). The patient completed six cycles of R-Benda. Twenty-three months later, after the first diagnosis of FL, during regular image check-ups, such as CT scans of the neck, chest, abdomen, and pelvis and PET scans, the patient was examined for multiple nodules that may have made a new appearance in the right supraclavicular (Fig. 3C), mediastinal, and abdominal cavity lymph nodes, as well as in the liver (Fig. 3D), spleen, or bilateral lungs, which is consistent with progressive disease. An incisional biopsy of the right supraclavicular lymph node and a needle biopsy of the mass in segment 5/8 of the liver were

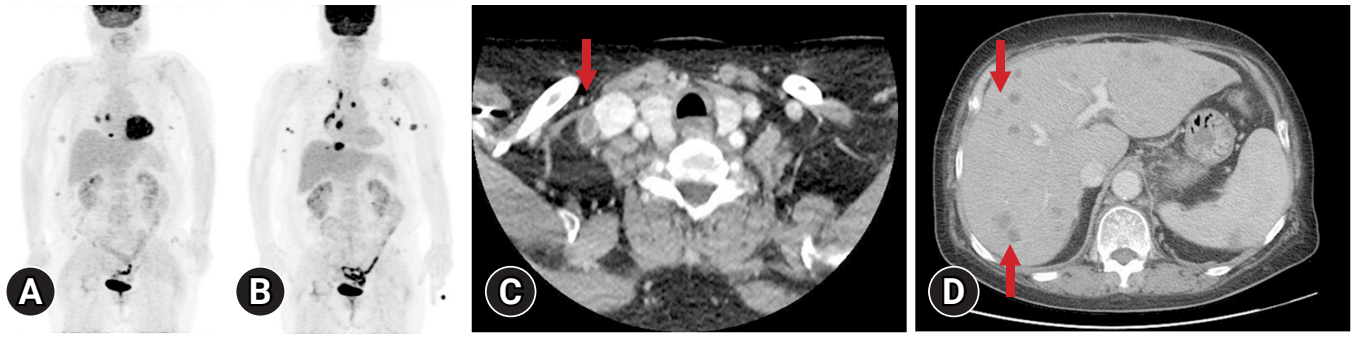

Fig. 3. Positron emission tomography (PET) images. (A) Stage workup revealing fluorodeoxyglucose uptake in bilateral posterior shoulder, back, flank, bilateral breast, left axilla, and diaphragmatic lesions. (B) PET during regular check-up after the diagnosis of follicular lymphoma shows a new lesion in the left supraclavicular, mediastinal, and left axillary lymph nodes. (C) Enlarged lymph nodes of the right supraclavicular area and lateral neck, exhibiting internal necrosis (arrow). (D) Abdomen computed tomography displaying multiple small low-density nodules in both livers (arrows).

performed to confirm the diagnosis.

At a low magnification of the supraclavicular lymph node specimen, the normal lymph node architecture was replaced by the proliferation of large histiocytoid cells with extensive necrosis (Fig. 4A) with the Reed-Sternberg cells being rarely observed in the background of the histiocytes and sparse lymphocytes (Fig. 4B, 4C). No follicular growth pattern and only a small number of lymphoid cells were observed. The Reed-Sternberg cells were positive for CD30 (Fig. 4D), PAX-5 (Fig. 4E), MUM1(Fig. 4F), and Bcl-2. Furthermore, the cells were negative for CD20, CD79a, CD15, anaplastic lymphoma kinase (ALK; also known as CD236), CD10, and cyclin D1, and the Bcl-6 antibodies reacted weakly to these cells (Fig. 4G). The *in situ* hybridization of the Epstein-Barr virus-encoded small RNAs (EBER ISH) was negative. The Bcl-2 translocation fluorescence *in situ* hybridization (FISH) using a Vysis Bcl-2 dual color, break-apart rearrangement probe (Abbott Molecular, Des Plaines, IL, USA) was negative for the Bcl-2 (18q21) translocation or copy number gain/amplification. The diagnosis was classical HL, an unclassifiable subtype, although some parts of the lesion resembled classical HL, a lymphocyte-depleted subtype.

The liver exhibited similar pathologic findings to those of the neck lymph nodes. The hepatic lesion displayed large cells accompanied by fibrosis, clearly distinguishable from the surrounding non-neoplastic hepatic parenchyma (Fig. 4H). Notably, the presence of Reed-Sternberg cells and Hodgkin cells was more frequent compared to the lymph node biopsy (Fig. 4I), with positive immunostaining observed for CD30, PAX-5, Bcl-6, Bcl-2, and MUM1. The Ki-67 labeling index was low, primarily expressed in Reed-Sternberg cells. Negative results were obtained for CD20, CD79a, ALK (CD246), and cyclin D1, as well as EBER ISH. Additionally, the Bcl-2 translocation FISH yielded negative results for Bcl-2 (18q21) translocation or copy number gain/amplification. The polymerase chain reaction (PCR) analysis for clonal immunoglobulin heavy chain (IgH) gene rearrangements was inconclusive, displaying a peak near the cutoff within the valid size range. Thus, the unclassifiable classical HL diagnosis was established for liver involvement as well.

Discussion

Despite the diagnostic limitations due to the impossibility of assessing all tissues of the first and second-time diagnosis, it is possible to state that the composite lymphoma of FL and classical HL recurred as a form of classical HL. To minimize diagnostic error, the submitted tissues were entirely embedded and reviewed several times. To rule out nodular lymphocyte-predominant HL, we re-examined the diagnosed FL and found no large tumor cells such as popcorn cells. In addition, large lymphoid cells of the supraclavicular and liver biopsies were positive for CD30 and negative for CD20, supporting the diagnosis of classical HL. Moreover, no T-cell rosettes were found. Large B cell lymphoma with interferon regulatory factor rearrangement was also ruled out because of MUM1 immunohistochemistry negativity. Here, we confirmed that pathological findings were quite different between the first and the second diagnoses, with the second and the third lesion appearing after the completion of the treatment.

Simultaneous, composite, or sequential occurrence of FL and classical HL, which both originate from germinal center B-cell, is rare. Compared with classical HLs, nodular lymphocyte-predominant HLs are associated more commonly with B-cell lymphoma. With regard to classical HL following FL, as in this case, Jaffe et al. [2] reported that lymphomas of HLs following FLs are the most frequent consequent lymphomas. This may have been due to the high incidence of FLs in Western countries. Notably, FLs do not

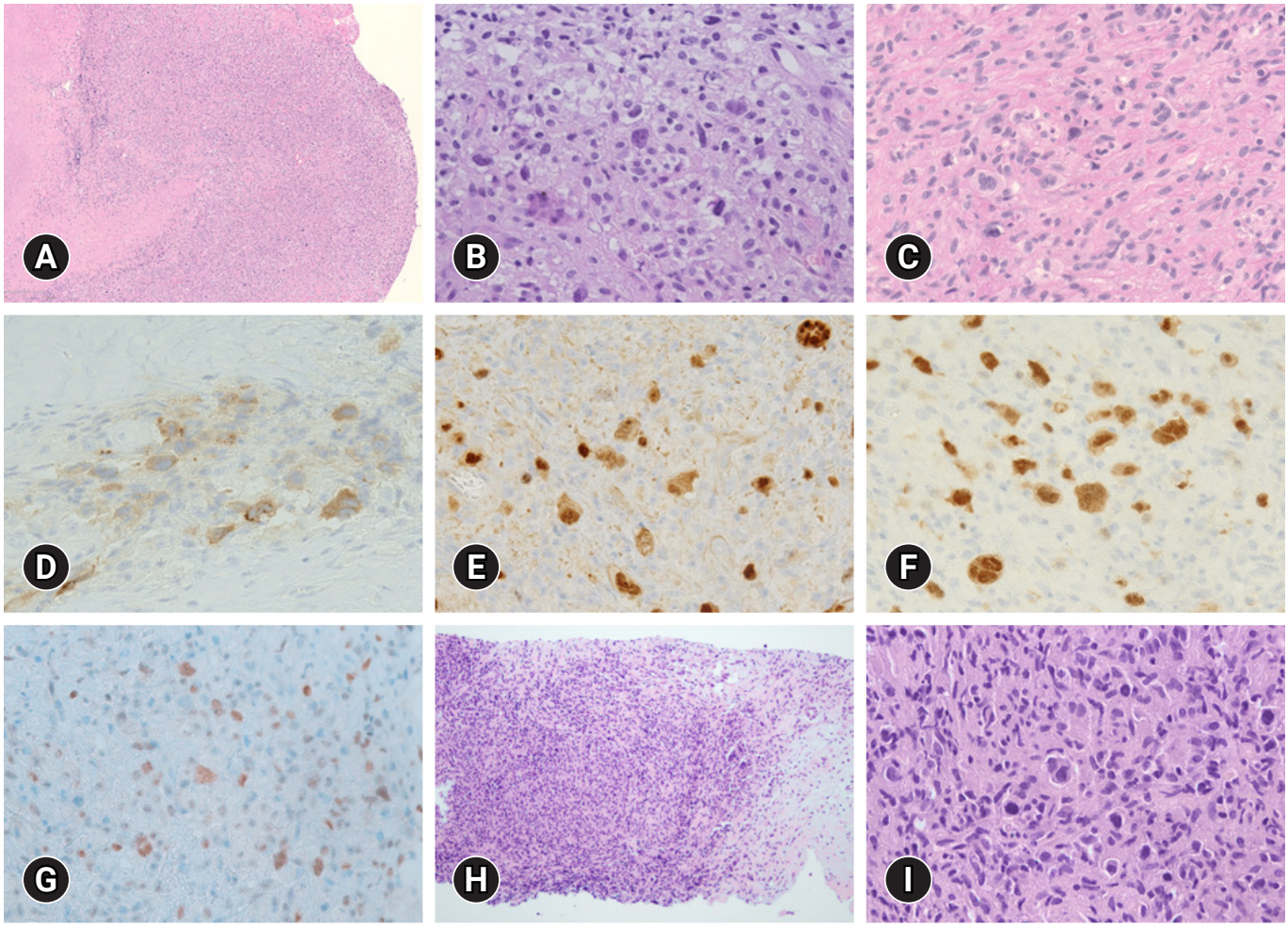

Fig. 4. Microscopic findings of the supraclavicular lymph node and liver. (A) Lymph node effaced by the proliferation of large histiocytoid cells with extensive necrosis (hematoxylin and eosin [H&E] stain, ×40). (B, C) High magnification view showing scattered Reed-Sternberg cells admixed with histiocytes (H&E stain, ×400). (D) CD30 immunohistochemistry revealing positive staining in Reed-Sternberg cells (CD30 immunohistochemistry, ×400). (E) Weaker to PAX-5 antibody reactivity in large cells compared to strongly positive non-neoplastic B-cells (PAX-5 immunohistochemistry, ×400). (F) MUM1 expression in the nuclei of tumor cells (MUM1 immunohistochemistry, ×400). (G) Weak expression of Bcl-6 in the nuclei of tumor cells (Bcl-6 immunohistochemistry, ×400). (H) Liver biopsy showing a nodular proliferation of lymphoid cells with fibrosis (H&E stain, ×100). (I) High-power view of the liver biopsy, revealing Reed-Sternberg cells and histiocytes identical to that of the lymph node biopsy (H&E stain, ×400).

occur in East Asia as often as they do in Western countries [3]. We have compiled 35 cases of classical HLs preceded by FLs by reviewing several original articles [4-17] (Table 1). Moreover, nine cases in China and Japan have been reported since 1996. Considering that the incidence of FL in South Korea is rising, it is important to report this case that occurred in our country [18].

HLs following FLs appeared in patients aged 27 to 89 years, and the time interval between the FLs and HLs ranged from 12 to 276 months. The HLs were observed as composite (two cases), simultaneous (three cases), or both composite and simultaneous (three cases), as well as pure classical HL (27 cases). It is generally accepted that FLs and HLs originate from transformed mutating and antigen-selected germinal center B-cells and preapoptotic germinal B-cells, respectively [19]. Some composite or sequential lymphomas exhibited shared genetic alterations, including translocation involving Bcl-2 or Bcl-6, or clonality of IgH or immunoglobulin kappa chain rearrangement These findings suggest neoplastic transdifferentiation occurring between the different components of the two lymphomas [20]. Trecourt et al. [20] reported that mutations in *BCL2, CREBBP, KMT2D, EP300*, and *ARID1A* are frequently observed in both sequential and composite lymphomas of FL and HL. These mutations, which are found usually in FLs but not in HLs, may serve as driver mutations in the development of these lymphomas. However, different mutations specific to each

Table 1. Summary of classical Hodgkin lymphomas (HL) following follicular lymphomas

No.	Case	Year	Age at initial diagnosis (yr)/sex	Initial diagnosis (site)	Initial therapy/response	Interval to transformation (time of relapse, mo)	Second diagnosis (site)	Second therapy/response	Follow-up from the initial diagnosis (mo)	Outcome
1	Custer and Bernhard [4]	1948	33/F (case 1)	FL (LN)	RT/NA	NA	HL (LN)	NA	23	DOD
2	Custer and Bernhard [4]	1948	NA	FL (LN)	NA/NA	NA	HL (LN)	NA	NA	DOD
3	Carrato et al. [5]	1987	68/F (case 2)	FL CCC (neck LN)	RT /CR	60	HL NS (left axillary LN, supraclavicular, portahepatic, paraaortic, peripancreatic, and mesenteric nodes; spleen; liver; left lung; left kidney; and BM)	Vinblastine, thiotepa, procarbazine, and prednisone+palliative RT/NC	62	DOD
4	Carrato et al. [5]	1987	40/M (case 3)	FL CCC (right submandibular and left inguinal LN) FL CCC or mantle cell lymphoma (left inguinal LN)	RT, chlorambucil/CR	276	HL NS (right inguinal node)	Cyclophosphamide, vincristine, procarbazine, and prednisone, (COPP) → lomustine, vinblastine, procarbazine, and prednisone → prednisone, lomustine, vinblastine, and procarbazine → lomustine, vinblastine, procarbazine, prednisone, and methotrexate/PD →CR	354	NED
5	Carrato et al. [5]	1987	74/M (case 5)	FL CCC (small bowel, retroperitoneum)	Surgery, RT (3500 rad) vincristine, cyclophosphamide, and chlorambucil/CR	92	Simultaneous: HL NS (left neck LN) FL CCC (BM)	MOPP-ABV-CAD/CR	120	NED
6	Lenner et al. [6]	1989	39/M	FL CCC and CBC (inguinal LN)	Oral prednomustine/CR	36	Composite: HL MC and FL CCC and CBC (spleen, hepatoduodenal, paraaortic and inguinal LNs)	Alternating MOPP and AVBD/PD	72	AWD
7	Gonzalez et al. [7]	1991	43/M (case 2, case 3 of Jaffe 1992)	DLBCL (NA) FL CCC and CBC (NA)	NA/NA	48	Simultaneous and composite HL UC, FL and DLBCL (inguinal LN) HL NS and DLBCL (90%) (supraclavicular LN)	CT, AMBT/PD	26	DOD
8	Gonzalez et al. [7]	1991	63/M (case 3)	FL CCC and CBC (NA)	NA	36	Composite: HL MC (10%) and DLBCL (90%) (stomach)	Surgery	2	DOD
9	Gonzalez et al. [7]	1991	48/M (case 8, case 1 of Jaffe 1992)	FL CCC and CBC (NA)	NA	144	Composite: HL NS and FL CCC and CBC (large cell 75%) (neck and inguinal LN) HL interfollicular type and FL CCC and CBC (large cell 90%) (submandibular LN)	RT, nitrogen mustard, vincristine, prednisone, procarbazine/PD	35	DOD

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Table 1. Continued

No.	Case	Year	Age at initial diagnosis (yr)/sex	Initial diagnosis (site)	Initial therapy/response	Interval to transformation (time of relapse, mo)	Second diagnosis (site)	Second therapy/response	Follow-up from the initial diagnosis (mo)	Outcome
10	Travis et al. [8]	1992	39/F (case 5)	FL CCC (NA)	CT	65	HL UC (LN)	NA	69	DOC
11	Travis et al. [8]	1992	57/F (case 6)	FL CCC and CBC (LN)	NA	137	HL NS (LN and BM)	NA	141	DOC
12	Zarate-Osorno et al. [9]	1993	27/F (case 1)	FL CCC and CBC (supraclavicular LN)	C-MOPP, CHOP, RT	96	HL NS (subxiphoid LN)	CT	114	DOD
13	Zarate-Osorno et al. [9]	1993	61/F (case 2)	FL CCC and CBC (neck LN)	Cyclophosphamide, prednisone, vincristine, procarbazine	48	HL NS (supraclavicular LN)	Cyclophosphamide, vincristine, prednisone, etoposide	66	NED
14	Zarate-Osorno et al. [9]	1993	72/M (case 3)	FL CBC (neck and intra-auricular LN)	Cyclophosphamide, prednisone, vincristine, RT	36	HL NS (inguinal LN)	RT	70	NED
15	Zarate-Osorno et al. [9]	1993	57/F (case 4)	FL CCC (inguinal LN)	Prednisone, chlorambucil	144	HL UC (periaortic LN, liver)	ABVD/MOPP, etoposide	153	NED
16	Zarate-Osorno [9]	1993	54/F (case 5)	FL CCC and CBC (femoral LN)	RT, chlorambucil, prednisone	60	HL NS (neck LN)	CT	60	NA
17	Zarate-Osorno et al. [9]	1993	36/M (case 7)	FL CCC (inguinal and axillary LN)	None	24	Simultaneous: HL MC (inguinal LN) FL CCC (inguinal LN)	ProMACE-MOPP, RT, AMBT	60	DOD
18	Zarate-Osorno et al. [9]	1993	36/F (case 8)	FL and DLBCL cell (Jejunum) FL, CCC (mesenteric LN)	ProMACE-MOPP	72	Simultaneous and composite: HL NS (periaortic LN) FL and DLBCL (mesenteric LN)	ProMACE CytaBOM RT	150	NED
19	LeBrun et al. [10]	1994	NA (HH)	FL CBC (NA)	RT	180	HL NS (NA) t (18;14)(+)	NA	NA	NA
20	LeBrun et al. [10]	1994	NA (HN)	FL CCC (NA)	RT	132	HL MC (NA) t (18;14)(+)	NA	NA	NA
21	LeBrun et al. [10]	1994	NA (VS)	FL CCC (NA)	CT	48	HL NS (NA) t (18;14)(–)	NA	NA	NA
22	LeBrun et al. [10]	1994	NA (BB)	FL CCC (NA)	NA	84	HL MC (NA)	NA	NA	NA
23	LeBrun et al. [10]	1994	NA (AL)	FL CCC (NA)	NA	84	HL MC (NA)	NA	NA	NA
24	LeBrun et al. [10]	1994	NA (LD)	FL CCC (NA)	NA	12	HL UC (NA)	NA	NA	NA
25	Hirose et al. [11]	1996	62/M	FL CCC (neck LN, duodenum) EBER(–)	CHOP #5/PD	16	Simultaneous: HL MC (inguinal, paraaortic, mesenteric, and along the lesser curvature LN) EBER(+) FL CCC (duodenum)	Surgery, CT	18	DOC
26	Thirumala et al. [12]	2000	60/M	FL, CCC (unspecified site)	RT	156	Composite: HL NS and FL CCC (inguinal LN)	NA	NA	NA
27	Copur et al. [13]	2004	68/F	FL CCC (10%) and CLL (90%) (BM) → FL (BM) FL CCC (inguinal, mesenteric, periaortic, pericaval, and liver)	SNOP #6 →fludarabine #6, rituximab #4/PR →PD→CR	96	HL (liver and retroperitoneal LN) t(14;18)(–)	Methylprednisolone → Liposomal doxorubicin #4/CR	NA	NA

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Table 1. Continued

No.	Case	Year	Age at initial diagnosis (yr)/sex	Initial diagnosis (site)	Initial therapy/response	Interval to transformation (time of relapse, mo)	Second diagnosis (site)	Second therapy/response	Follow-up from the initial diagnosis (mo)	Outcome
28	Nakamura et al. [14]	2007	44/M	FL grade 1 (abdominal cavity) EBER(–), t(14;18)(+)	NA	48	HL MC (neck LN) EBER(–), t(14;18)(+)	NA	NA	NA
29	Yoshida et al. [15]	2012	63/M (case 3)	FL, grade 3A (inguinal LN)	NA	120	HL MC (systemic) EBER(–), translocation of 18q21 (+)	NA	NA	NA
30	Yoshida et al. [15]	2012	89/F (case 4)	FL grade 1 (colon) EBER(–), t(14;18)(+)	NA	36	HL MC (neck LN) t(14;18)(+)	NA	NA	NA
31	Wang et al. [16]	2016	63/M (case 2)	FL (site unspecified), stage IV	R-CVP #6/PD	72	HL (paraaortic and retroperitoneal LNs)	NA/NA	NA	NA
32	Wang et al. [16]	2016	53/M (case 3)	FL grade 3, stage IV t(14;18)(+) FL grade 2 (lung)	R-CHOP #8/CR	66	HL NS (mediastinal LN) t(14;18)(+) t-MDS (BM)	CT #2, Auto-SCT/PD	0	DOD
33	Wang et al. [16]	2016	48/M (case 4)	FL grade 1 (inguinal LN) IgH(+) t(14;18)(+)	R-Benda #4 R-CHOP #6/PD	24	HL NS (paraaortic, retroperitoneal, peribiliary LNs) IgH+ t(14;18)+	None	0	DOC
34	Wang et al. [16]	2016	68/M (case 5)	FL grade 1–2 (inguinal LN) IgH(+)	R-Benda ibritumomab tiuxetan/PD	12	Composite: HL NS (axillary LN) IgH(+) t(14;18)(+) FL low grade (inguinal LN)	ABVD #3 → brentuximab and then gemcitabine, vinorelbine, and doxorubicin → RICE → brentuximab → ipilimumab and nivolumab/PD	48	AWD
35	Tennese et al. [17]	2017	49/M	FL, grade 3A, SLL, and MCLIS (left inguinal LN) EBER(–) IgH(+) t(14;18)(+) in FL 14q32/IgH translocation in SLL CCND1/IgH translocation in MCLIS FL grade 1–2, SLL (submental LN)	CHOP #6 → fludarabine, chlorambucil, and rituximab → autologous stem cell transplant/PR → CR	144	HL MC (right axillary LN) EBER(–) IgH(+), a different peak from previous FL	ABVD #4 →gemcitabine and vinorelbine/CR →PD	168	DOC (sepsis)

F, female; FL, follicular lymphoma; LN, lymph node; RT, radiotherapy; NA, not applicable; DOD, died of disease; CCC, centrocytic type; NS, nodular sclerosing; NC, non-curative; M, male; CR, complete remission; COPP, cyclophosphamide, oncovin, procarbazine, prednisone; PD, progressive disease; NED, no evidence of disease; MOPP, nitrogen mustard, vincristine, procarbazine, prednisone; ABV, adriamycin (doxorubicin), bleomycin, vinblastine; CAD, comustine, alkeram, diacetylvinblastine (vindesine); MC, mixed cellularity; AVBD, adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine; AWD, alive with disease; DLBCL, diffuse large B-cell lymphoma; CBC, centroblastic type; UC, unclassifiable; CT, computed tomography; DOC, died of complications or died of other cause; BM, bone marrow; AMBT, autologous bone marrow transplantation; ProMACE-MOP, prednisone, methotrexate, adriamycin (doxorubicin), cyclophosphamide, etoposide-mustargen (mechlorethamine), oncovin (vincristine), procarbazine, prednisone; CytaBOM, cytarabine, bleomycin, vincristine (oncovine), methotrexate; EBER, Epstein-Barr virus (EBV)-encoded small RNA; CLL, chronic lymphocytic leukemia; SNOP, cyclophosphamide, mitoxantrone, vincristine, prednisone; PR, partial response; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; t-MDS, therapy-related myelodysplastic syndrome; SCT, stem cell transplantation; IgH, immunoglobulin heavy chain; R-Benda, rituximab-bendamustine; RICE, rituximab, ifosfamide, carboplatin, etoposide; SLL, small lymphocytic lymphoma; MCLIS, mantle cell lymphoma *in situ*; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CCND1, cyclin D1.

contingent may have been secondary or passenger mutations [20]. Thus, it is plausible that this particular case also exhibited genetic alterations shared between FLs and HLs, although these specific alterations were not assessed in this study.

In our cases, we considered the pathological diagnosis to be an anaplastic variant of DLBCL, HL, anaplastic large-cell lymphoma, or FL showing anaplastic large-cell lymphoma-like features with a treatment effect. The negative result for both CD20 and CD79a ruled out the diagnosis of B-cell lymphoma, and a low Ki-67 labeling index eliminated the possibility of DLBCL. Furthermore, an anaplastic large-cell lymphoma was excluded based on the PAX-5 expression. Given that the IgH rearrangement clonality and *BCL2* gene translocation may sometimes be found in both HLs and FLs of consequent lymphoma [10,14-17,20], pathologists should not rely on them for molecular investigations. While HLs and FLs have been shown to have different peaks in IgH gene rearrangement PCR, they were observed to have IgH clonality [17]. Notably, the most crucial point was using a basic morphologic assessment, such as assessing the Reed-Sternberg cells, background cells, and growth patterns.

We presented a case of HL that occurred 23 months after FL. The FL and HL originated from germinal center B-cells. Sequential or composite FL and HL sometimes share common genetic alterations, which supports the idea that they shared identical clones and that transdifferentiation may cause composite or sequential lymphomas. Clinical, histological, immunohistochemical, and molecular investigations are critical for a correct diagnosis.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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ORCID

Bomi Kim, https://orcid.org/0000-0003-3776-8622

References

1. Lossos IS, Gascoyne RD. Transformation of follicular lymphoma. Best Pract Res Clin Haematol 2011;24:147–63.
2. Jaffe ES, Zarate-Osorno A, Medeiros LJ. The interrelationship of Hodgkin's disease and non-Hodgkin's lymphomas: lessons learned from composite and sequential malignancies. Semin Diagn Pathol 1992;9:297–303.
3. Huh J. Epidemiologic overview of malignant lymphoma. Korean J Hematol 2012;47:92–104.
4. Custer RP, Bernhard WG. The interrelationship of Hodgkin's disease and other lymphatic tumors. Am J Med Sci 1948;216:625–42.
5. Carrato A, Filippa D, Koziner B. Hodgkin's disease after treatment of non-Hodgkin's lymphoma. Cancer 1987;60:887–96.
6. Lenner P, Roos G, Hedenus M, Lindh J. Simultaneous presentation of relapsing non-Hodgkin's lymphoma and Hodgkin's disease. Eur J Haematol 1989;42:315–6.
7. Gonzalez CL, Medeiros LJ, Jaffe ES. Composite lymphoma: a clinicopathologic analysis of nine patients with Hodgkin's disease and B-cell non-Hodgkin's lymphoma. Am J Clin Pathol 1991;96:81–9.
8. Travis LB, Gonzalez CL, Hankey BF, Jaffe ES. Hodgkin's disease following non-Hodgkin's lymphoma. Cancer 1992;69:2337–42.
9. Zarate-Osorno A, Medeiros LJ, Kingma DW, Longo DL, Jaffe ES. Hodgkin's disease following non-Hodgkin's lymphoma: a clinicopathologic and immunophenotypic study of nine cases. Am J Surg Pathol 1993;17:123–32.
10. LeBrun DP, Ngan BY, Weiss LM, Huie P, Warnke RA, Cleary ML. The bcl-2 oncogene in Hodgkin's disease arising in the setting of follicular non-Hodgkin's lymphoma. Blood 1994;83:223–30.
11. Hirose Y, Iwabuchi K, Shimizu S, Sasaki K, Nojima T, Takiguchi T. Nodal EBV-positive Hodgkin's disease following extranodal EBV negative non-Hodgkin's lymphoma of B-cell lineage. Eur J Haematol 1996;57:103–6.
12. Thirumala S, Esposito M, Fuchs A. An unusual variant of composite lymphoma: a short case report and review of the literature. Arch Pathol Lab Med 2000;124:1376–8.
13. Copur MS, Ledakis P, Novinski D, Fu K, Hutchins M, Frankforter S, et al. An unusual case of composite lymphoma involving chronic lymphocytic leukemia follicular lymphoma and Hodgkin disease. Leuk Lymphoma 2004;45:1071–6.
14. Nakamura N, Ohshima K, Abe M, Osamura Y. Demonstration of chimeric DNA of bcl-2 and immunoglobulin heavy chain in follicular lymphoma and subsequent Hodgkin lymphoma from the same patient. J Clin Exp Hematop 2007;47:9–13.
15. Yoshida M, Ichikawa A, Miyoshi H, Takeuchi M, Kimura Y, Nino D, et al. High frequency of t(14;18) in Hodgkin's lymphoma associated with follicular lymphoma. Pathol Int 2012;62:518–24.
16. Wang XJ, Griffin GK, Yenamandra A, Wheeler FC, Ligon AH, Nandedka MA, et al. Transformation of follicular lymphoma

into classical Hodgkin lymphoma showing t(14;18). Hematopathology 2016;1:23–33.
17. Tennese A, Skrabek PJ, Nasr MR, Sekiguchi DR, Morales C, Brown TC, et al. Four lymphomas in 1 patient: a unique case of triple composite non-Hodgkin lymphoma followed by classical Hodgkin lymphoma. Int J Surg Pathol 2017;25:276–80.
18. Kim M, Hwang HS, Cho H, Yoon DH, Suh C, Park CS, et al. Upward trend in follicular lymphoma among the Korean population: 10-year experience at a large tertiary institution. J Pathol Transl Med 2021;55:330–7.
19. Küppers R, Sousa AB, Baur AS, Strickler JG, Rajewsky K, Hansmann ML. Common germinal-center B-cell origin of the malignant cells in two composite lymphomas, involving classical Hodgkin's disease and either follicular lymphoma or B-CLL. Mol Med 2001;7:285–92.
20. Trecourt A, Mauduit C, Szablewski V, Fontaine J, Balme B, Donzel M, et al. Plasticity of mature B cells between follicular and classic Hodgkin lymphomas: a series of 22 cases expanding the spectrum of transdifferentiation. Am J Surg Pathol 2022;46:58–70.