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Original Article

Development of follicular lymphoma after treatment of diffuse large B-cell lymphoma: two case reports with review of literature

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Abstract: Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent subtypes of aggressive lymphomas, which can be transformed lymphoma that mostly develops from other types of lymphoma. Cases of DLBCL arising developing after the initial diagnosis of follicular lymphoma (FL) have been reported. However, until now, little few studies have been reported were conducted on the patients with DLBCL and with subsequent development of FL in patients with DLBCL. Here we presented this study with two rare cases of, namely, FL and Composite concurrently occurs with DLBCL and FL developing after the initial diagnosis of DLBCL. In order to investigate the clinical and molecular features of patients with DLBCL and FL, we also reviewed the literature on FL patients with FL developing DLBCL, and patients with composite FL and DLBCL.

Keywords: Diffuse large B-cell lymphoma, follicular lymphoma, composite lymphoma

Introduction

Diffuse large B-cell lymphoma (DLBCL) is one of the most common Non-Hodgkin's lymphoma in clinical practice and is primarily derived from other types of lymphoma. Follicular lymphoma (FL) transforming to DLBCL is the most often reported case. To our best knowledge, the development of FL after treatment of DLBCL has not been reported yet.

A second lymphoma differs from the original lymphoma; the mechanism between the two distinct morphological types of lymphoma has attracted interests from hematologists because of the varying prognosis among affected patients. Studies have reported some cases of DLBCL (t-FL) that developed in patients with FL [1-8]. A review of the literature shows a small number of patients with composite FL and DLBCL [2, 9]. Scholars have proposed several hypotheses to explain the occurrence of clonal proliferations; this phenomenon could be due to chronic antigenic stimulation, such as viral infection and genetic changes caused by chemotherapy [10]. For example, Epstein-Barr virus is a possible etiological agent involved in the development of B-cell lymphoma after an existing T-cell lymphoma [11, 12]. Although the transformation of FL to DLBCL is commonly observed in clinical practice and several studies aim to determine the underlying pathogenesis, the precise mechanism remains unknown. Casulo et al [13] revealed that FL possibly originates from a series of natural transformations. The initiation of IGH/BCL2 translocation in early B cells and subsequent accumulation of oncogenic mutations producing FL occur through the mistargeted activity of activation-induced deaminase (AID); this protein is expressed in precursor FL cells and iteratively resides in germinal centers (GCs) in lymph nodes. AID expression in normal GCs induces somatic hypermutation of immunoglobulin loci, leading to B-cell malignancies that originate from follicular B cells. Suppressing AID expression causes genetic instability and potentially prevents the progression of FL. However, this mechanism cannot sufficiently explain the development of FL after DLBCL.

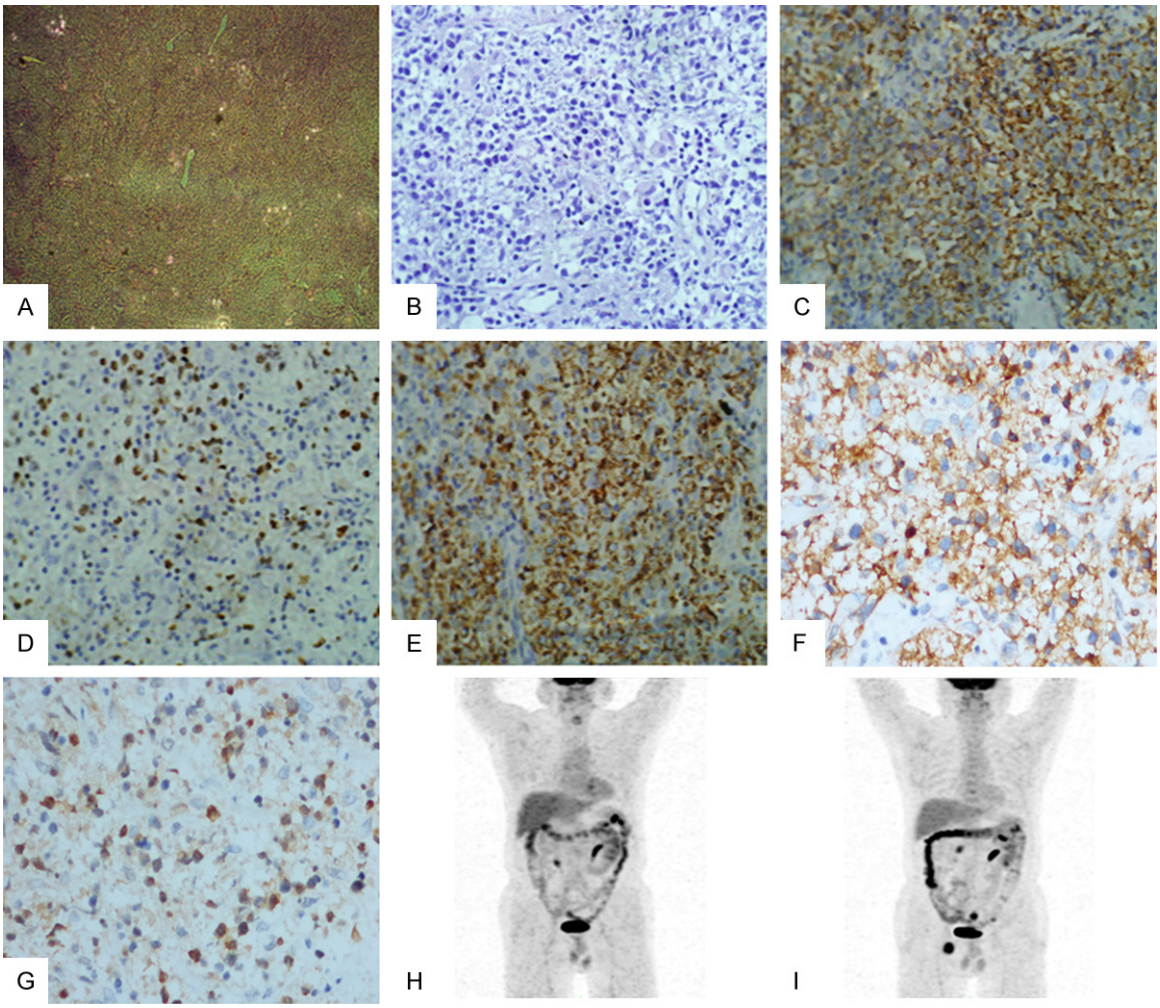

Figure 1. Initial biopsy from case 1 showing morphological (A, B) and immunohistochemical findings with positivity for CD20 (C), Ki67 (D), CD79α (E), CD10 (F), BCL-6 (G). PET-CT of the whole body disclosed mediastinal lymph nodes, metabolism is not high (H). Enlargement of the inguinal lymph nodes demonstrated by PET-CT (I) confirmed disease progression in August 2013. (A: H&E staining, with original magnification × 40; B: H&E staining, with original magnification × 400; C-G: immunohistochemical staining, with original magnification × 400).

In this study, we report two rare cases of FL developing after the initial diagnosis of DLBCL We also present a literature review on cases of patients with FL developing DLBCL and patients with composite FL and DLBCL. We summarize the clinical and pathological features of both groups of patients.

Case presentation

Case 1

A 64-year-old man with abdominal distension was admitted to our hospital in August 2010. The abdominal ultrasound result showed a huge retroperitoneal mass. Positron emission tomography and computed tomography (PET-CT) analysis of the whole body disclosed retroperitoneal huge mass (19 cm × 7.9 cm × 8.3 cm). Biopsies of the huge mass revealed the diagnosis of DLBCL. The nodal structure was partly effaced by a diffuse proliferation of large lymphoid cells (**Figure 1A** and **1B**). Immunohistochemical staining patterns demonstrated that lymphoid cells expressed CD20 (**Figure 1C**) and exhibited high proliferation rate measured by Ki67 (**Figure 1D**). These cells were also positive for CD79a, CD10, and BCL-6 expression (**Figure 1E-G**) but negative for CD3, CD7, CD30 and Mum1 expression (data not shown). Polymerase chain reaction analysis of the IgH and TCR genes revealed no clonal rearrangements (Supplementary Figure 1A-C). After completing four cycles of R-CHOP (rituximab, cyclophosphamide, pirarubicin, vindesine and

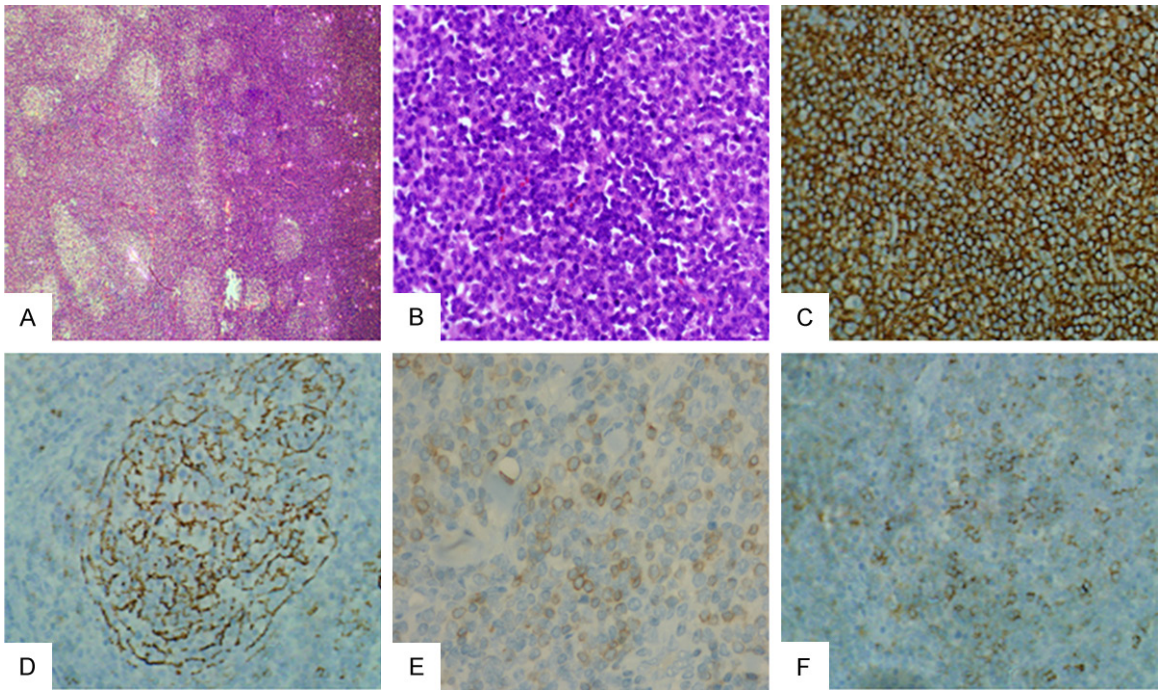

Figure 2. Follow-up biopsy from case 1 showing morphological (A, B) and immunohistochemical findings with positivity for CD20 (C), CD21 (D), BCL-2 (E), CD23 (F). (A: H&E staining, with original magnification × 40; B: H&E staining, with original magnification × 400; C-F: immunohistochemical staining, with original magnification × 400).

dexamethasone) chemotherapy, the patient did not achieve complete remission. After another three cycles of R-CHOP chemotherapy and 28 cycles of radiotherapy, the patient finally achieved complete remission as determined by PET-CT analysis (**Figure 1H**). However, PET-CT scanning in August 2013 showed the enlargement of the inguinal lymph nodes, confirming the progression of the disease (**Figure 1I**). After 1 week, biopsy of the enlarged right inguinal lymph node was performed. The results revealed FL (**Figure 2A** and **2B**). The lymphoid cells were tested positive for CD20, CD21, BCL-2 (**Figure 2C-E**) and CD23. Staining showed the presence of residual follicular dendritic cells (**Figure 2F**) and Ki67 assessment indicated low cell proliferation. A diagnosis of FL was established. The clonal rearrangements of the IgH and TCR genes were not found (Supplementary Figure 1D-F). The patient was subjected to two cycles of RCOP and four cycles of rituximab. The patient remained in remission up to June 2015.

Case 2

A 69-year-old woman with multiple enlarged lymph nodes in the neck, mandible and inguinal areas was admitted to our hospital in April 2012. The PET-CT scan of the whole body showed generalized lymphadenopathy in the neck, axillae, chest and inguinal areas. Biopsies of the enlarged inguinal lymph node revealed the diagnosis of DLBCL. The diagnosis was confirmed by morphological, immunohistochemical and molecular evaluation of the lymph node (**Figure 3A-G**; **Table 1**). Meanwhile, analyses of the IgH and TCR genes revealed no clonal rearrangements (Supplementary Figure 1G-I). After completing four cycles of R-CHOP+MTX (rituximab, cyclophosphamide, pirarubicin, vindesine, dexamethasone, and methotrexate) chemotherapy, the patient achieved complete remission as determined by PET-CT analysis (**Figure 3H**). The biopsy of the enlarged inguinal lymph node and bone marrow showed no evidence of lymphoma cells. The patient underwent another two cycles of R-CHOP and two cycles of RCOP (rituximab, cyclophosphamide, vindesine and dexamethasone) for consolidation therapy. Follow-up in October 2013 showed the enlargement of the inguinal lymph nodes, confirming the progression of the disease. The PET-CT (**Figure 3I**) scan of the whole body showed generalized lymphadenopathy in the submandibular and inguinal areas. The patient failed to respond to the salvage regimen CHOPE (rituximab, cyclophosphamide, pirarubicin, vin-

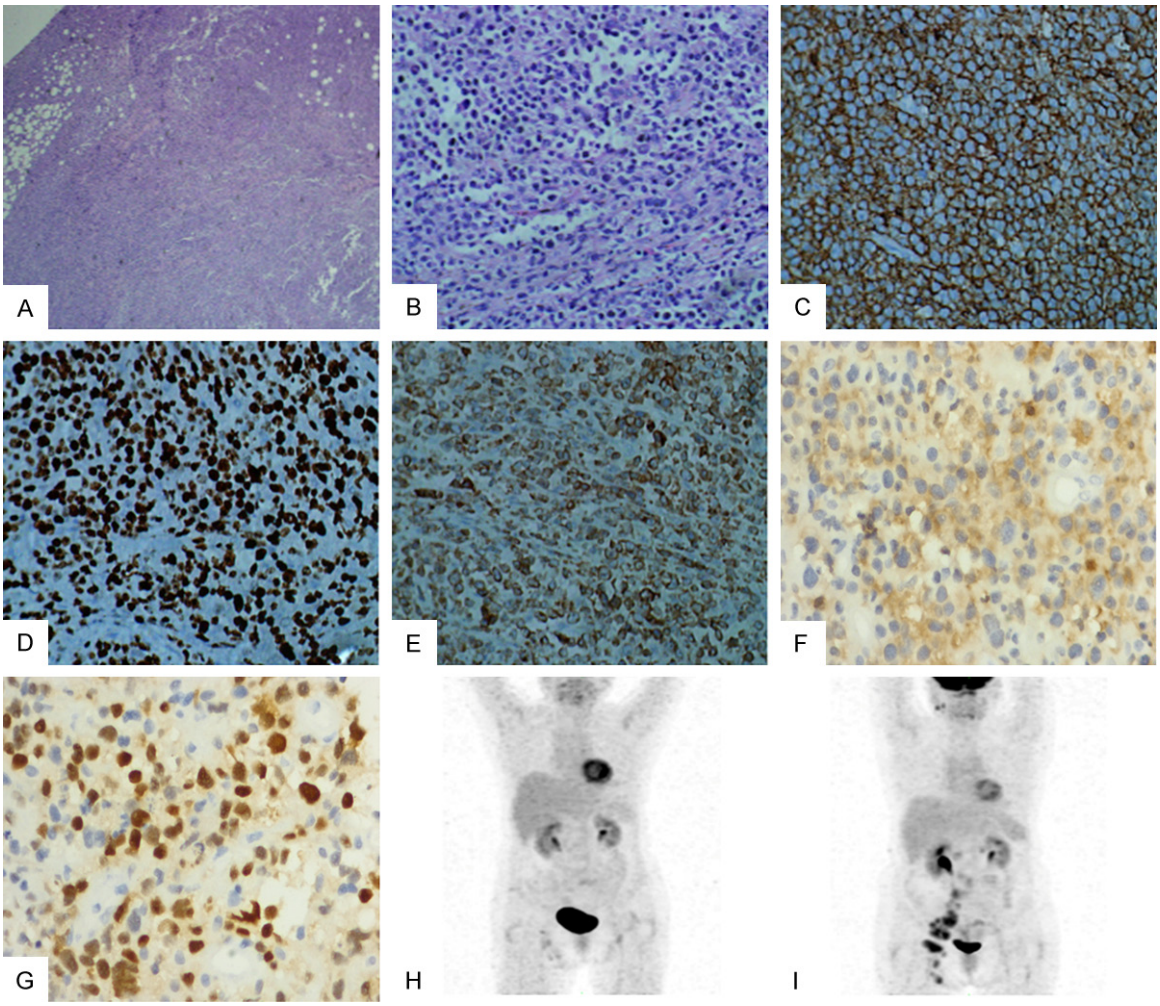

Figure 3. Initial biopsy from case 2 showing morphological (A, B) and immunohistochemical findings with positivity for CD20 (C), Ki67 (D), Bcl-2 (E), CD10 (F), BCL-6 (G). PET-CT of the whole body disclosed inguinal lymph nodes, metabolism is not high (H). Enlargement of the inguinal lymph nodes and submandibular lymph nodes lymph nodes demonstrated by PET-CT (I) confirmed disease progression. (A: H&E staining, with original magnification × 40; B: H&E staining, with original magnification × 400; C-G: immunohistochemical staining, with original magnification × 400).

desine, dexamethasone and etoposide). In December 2013, the biopsy of the enlarged right inguinal lymph node revealed DLBCL (25%) compositing with FL (75%). Histopathological analysis revealed diffuse infiltration of malignant neoplastic lymphoid cells (**Figure 4A**, **4B**). The lymphoid cells were tested positive for CD20 (**Figure 4C**), Bcl-2 (**Figure 4D**), Bcl-6 (**Figure 4E**) and CD21 (**Figure 4F**). Staining indicated the presence of residual follicular dendritic cells. The cells showed high proliferation rate as measured by Ki67 and tested negative for CD3 and CD5. Clonality analysis of the LN biopsy revealed the clonal rearrangement of IgH-DH and Igκ-V/in (Supplementary Figure 2A, 2B). Thus, a diagnosis of DLBCL compositing with FL was established. The patient was subjected to one cycle of rituximab and dexamethasone and two cycles of rituximab and fludarabine. However, the patient did not achieve complete remission although the superficial lymph nodes became smaller. Considering obvious bone marrow suppression after chemotherapy and pneumonia, doctors continued to treat the primary disease of the patient by oral prednisone. The patient succumbed to her disease at the end of October 2014.

Discussion

In this article, we present a unique case of FL developing 3 years after the initial diagnosis of DLBCL (case 1) and a case of sequential development of composite DLBCL and FL in a patient

Table 1. Summary of the morphological, immunophenotypical and molecular features of these two cases

		Initial biopsy	Follow-up biopsy
Case 1	Morphology	Typically sheets of centroblasts (abdominal mass)	Follicular pattern of growth (LN)
	Immunotistochemistry	CD20+ CD10+ CD79a+ Bcl-6+ Ki67+ (60%)	CD20+ BCL2+ CD21+ CD23+ Ki67+ (20%)
		CD30- Muml- CD3- CD7- CD21-	BCL6- Cyclin D1-
	Molecular features	IgH- TCR- EBER-	IgH- TCR- EBER-
Case 2	Morphology	Diffuse large cells (LN)	Intrafollicularneoplasia composite with diffuse large cells (LN)
	Immunotistochemistry	CD20+ CD10+ CD79a+ BCL6+ Ki67+ (80%)	CD20+ BCL2+ BCL6+ Ki67+ (80%)
		CD30- Muml- CD3- CD7- CD21-	CD21+ Muml±
	Molecular features	Fish: IgH- BCL2,	Fish: IgH- BCL2,
		Bcl-6, P53, MYC normal	Bcl-6, MYC normal
		IgH- TCR-	Clonal IgK-V/in, IgH-DH

EBER-ISH, Epstein-Barr virus-encoded RNA in situ hybridization; FISH, Fluorescence in-situ hybridization; FR1, Framework region 1; FR2, framework region 2; IgH, immunoglobulin heavy chain gene rearrangement; IgK, Immunoglobulin K; LN, lymph node; TCR, T-cell receptor rearrangement.

with DLBCL (case 2). For these two cases, the initial diagnosis was DLBCL and was confirmed by assessment of morphological and molecular features. The patients were given with different regimens of therapy, and both of them achieved complete remission. DLBCL is the most frequent subtype of aggressive lymphomas and accounts for a large proportion of clinical lymphoma. Hence, the development of a second lymphoma after treatment of DLBCL has gained increased research attention from hematologists.

A second FL developing in patients after the initial diagnosis of DLBCL has not been reported yet, although many patients with the initial diagnosis of FL have developed DLBCL (**Table 2**) [1-8]. In all documented cases, the interval from the initial diagnosis of FL to the development of DLBCL ranged from 6 months to 22 years. Alvaro-Naranjo T [1] reported a case of CD20-negative DLBCL transformation after rituximab treatment of follicular lymphoma; the patient died 12 months after the diagnosis of DLBCL that developed from FL. The survival rate of patients with this case is lower than that of patients tested positive for CD20. Moreover, patients with DLBCL originating from FL manifested clonal (monoclonal and oligoclonal) *IgH* gene rearrangements. These patients also featured a number of recurring cytogenetic abnormalities, including mutations of TP53 [14, 15]; deletions in CDKN2A/B [14]; mutations, translocations, or amplifications of MYC [16, 17]; and mutations or translocations of Bcl-2 [16-18] and Bcl-6 [16, 19]. Bcl-2 and Bcl-6 are the strongest predictors of patient survival [20]. As such, scholars must investigate the survival of patients with DLBCL developing after the diagnosis of FL.

Composite lymphoma refers to the co-occurrence of two or more morphologically and immunophenotypically separated lymphomas in the same topographic site at the time of clinical presentation. This type of lymphoma is an infrequent type of lymphoid neoplasm [9]. **Table 3** summarizes six cases of composite DLBCL and FL, including the presented case 2. FL was categorized as high grade (FL IIIA-B) in cases with composite lymphoma, especially in case 1, where three lymphomas were found in a single lymph node [9]; these lymphomas were formed from one low-grade lymphoma (FL I-II) and two high-grade lymphomas (FL IIIA and DLBCL). As shown in **Table 3**, the prognosis of these patients was generally poor, varying from only 11 months to 42 months, compared with that of patients shown in **Table 2** (two patients lost contact). The prognosis of the patients could be due to the staging and type of the disease.

FL is an incurable but indolent lymphoma with high survival rates, whereas DLBCL is characterized by an aggressive behavior with good response to chemotherapy [21]. Therefore, the therapy regimens for these lymphomas are different. The varying outcomes of the patients may be related to the stage of the initial diagnosis of FL and the kind of treatment they received (**Table 2**). Lerch K [7] reported 50 cases of DLBCL that developed after FL; the patients were all treated by combination chemotherapy, and the median follow-up was 1.9 years. Wirk B [8] analyzed the outcomes of transplant in 141 subjects with DLBCL that originated from FL; the median follow-ups of autoHCT and alloHCT were 85 and 64 months. The outcomes of transplant, especially that of autotransplant are more durable than non-transplant therapies, a prospective study must be conducted

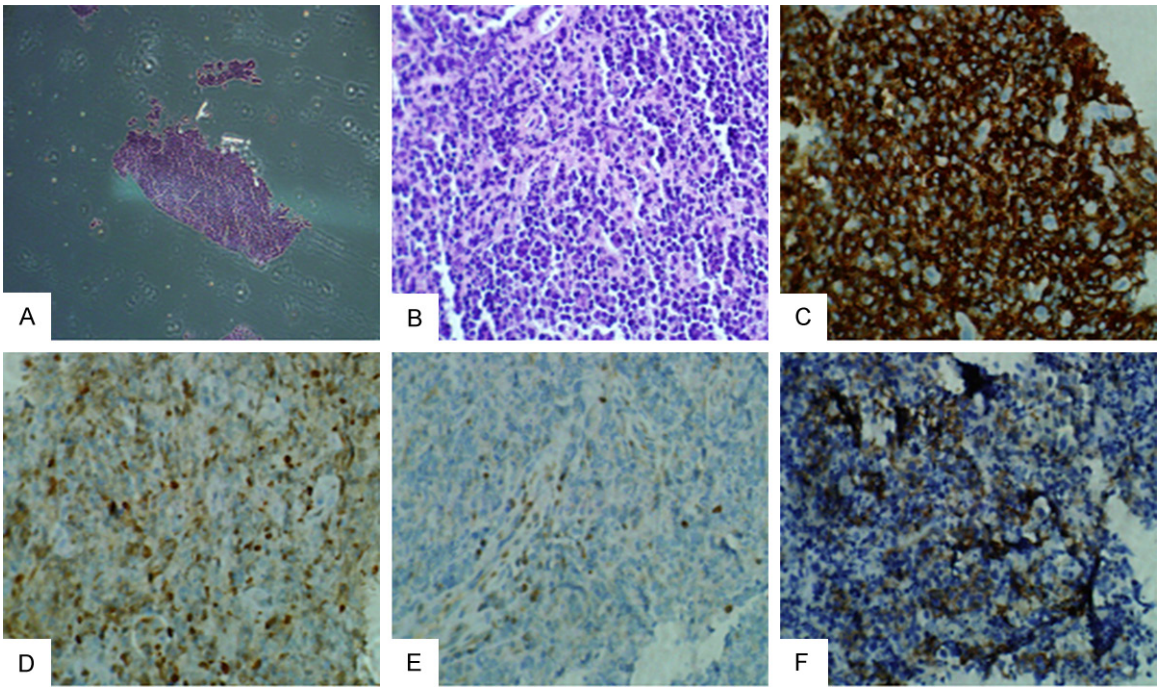

Figure 4. Follow-up biopsy from case 2 showing morphological (A, B) and immunohistochemical findings with positivity for CD20 (C), Bcl-6 (D), Bcl-2 (E) and CD21 (F). (A: H&E staining, with original magnification × 40; B: H&E staining, with original magnification × 400; C-F: immunohistochemical staining, with original magnification × 400).

to determine the feasibility of performing transplant prior to combination chemotherapy or rituximab combined with chemotherapy. Scholars must also investigate whether autoSCT provides better prognosis than alloSCT in these cases. Thus far, no unified regimens for FL that developed from DLBCL or composite FL and DLBCL have been developed.

Table 3 shows that the outcomes of patients who underwent CHOP chemotherapy are better than those without CHOP. This finding confirms the superiority of regimens containing CHOP. Additional cases must be analyzed to develop effective therapy protocols.

Studies have generally reported the development of DLBCL after FL and their proliferation mechanism. The presented cases are unique because FL developed after treatment of DLBCL. Despite differences in their morphology and clinical behavior, FL and DLBCL share similarities. For example, both FL and DLBCL develop from GC B cells. Genetic alterations, such as the overexpression and mutation of BCL2, greatly contribute to the cancer development of DLBCL; moreover, CXCR4 expression and PI3K signaling play an important role in FL [22]. These phenomena might explain the mechanism of the development of FL after DLBCL.

In conclusion, we presented two rare cases of a second lymphoma that developed after the initial diagnosis of DLBCL. Both tumors showed a GCB-type profile with immunohistochemical expressions of CD20, CD10, and Bcl-6. Patient in case 1 developed FL (low grade) after treatment of DLBCL and remains in remission to date. By contrast, patient in case 2 developed composite FL (high grade) and DLBCL after treatment of DLBCL and died of disease progression. Based on these two cases, prognosis was found to be related to the staging of FL. A review of the literature on patients developing DLBCL after the initial diagnosis of FL suggested poor prognosis of the patients. In the article published in BLOOD, Casulo et al [13] reported that hematologists can target mechanisms underlying continuous genetic instability (such as inhibiting AID) to prevent the progression of FL. This study brought the possibility of preventing the progression of transformed FL. Further studies must verify the possibility of transforming DLBCL to FL and whether this transformation can improve the clinical outcome of FL developing after DLBCL. Comparison of biopsy material from the same

Table 2. Summary of development of DLBCL after FL

Author	Case No.	No. of patients	Diagnosis	Time to follow-up diagnosis (M)	Biopsy site	Immunohistochemistry	IgH	Treatment	Outcome
Alvaro-Naranjo T [1]	1	1	FL	0	NA	CD20+	NA	CHOP rituximab	
			DLBCL	8 y	Liver and duodenal	CD20- CD79a+ CD45+ BCL6+	+	MINE ESHAP	Died, 12 months
Manazza AD [2]	1	1	FL	0	NA	CD5+ CD21+ CD19+ CD20+ CD10+	NA	MACOP-B	
			DLBCL	3 y	NA	CD5+ CD19+ CD20+ CD10+ Cyclin D1-	+	HDS+ABMT	Died, 26 Months
Vassallo J [3]	1	1	FL	0	Inguinal lymph node	CD20+ CD79a+ BCL2+ BCL6+ CD5+ CD10+ Ki-67+ (>70%)	+	NA	
			DLBCL	6 m	Spinal lymph node	CD20+ CD79a+ BCL2+ BCL6+ CD6+ CD10± Ki-67+ (<10%)	+	NA	NA
Maeshima AM [4]		107	FL	0	NA	NA	NA	NA	
			DLBCL/ FL+DLBCL	23 m	NA	CD10+ 64%; BCL2+ 83%; BCL6+ 88%; MUM1+ 42%; GCB+ 82%	+	R-CHOP	Median follow-up were 70 m (2-162 m)
Miyata-Takata T [5]	1	1	FL	0	Duodenum	CD20+ CD3- CD10+ BCL2+ MYC- Ki67+ (<5%)	+	Watch-and-wait	
			DLBCL	62 m	Duodenum	CD20+ CD3- CD5- CD10+ BCL2+ MYC+ Ki67+ (>90%)	+	Half dose of THP-COP	NA
Montes-Moreno S [6]	1	2	FL	0	BM	CD20+ CD10+ CD30-	+	Immunochemotherapyin-trathecal therapy	
			DLBCL	NA	LN	CD20+ CD30+ CD10+ (>30%) BCL2+ (>50%) BCL6+	+	BEAM+auto-SCT	AWOD 1 y
	2		FL	0	Tonsil	CD20+ CD10+ BCL2+ Ki67+ low, CD30-	+	NA	
			DLBCL	NA	Tonsil	CD20+ CD30+ BCL2+ (>50%) BCL6+ (>30%) MUM1+	+	R-CHOP	NA
Lerch K [7]		50	FL	0	NA	NA	NA	Chemotherapy 74%, radiotherapy	
			DLBCL	5.8 y (0.5-22)	NA	NA	NA	CHOP DHAP ICE DHOx et al	Median follow-up were 1.9 y
Wirk B [8]		141	FL	0	NA	NA	NA	NA	
			DLBCL	NA	NA	NA	NA	auto-SCT 77% allo-SCT 23%	Median follow-up were 85 m and 64 m

ABMT, allogeneic bone marrow transplantation; auto-SCT, autologous stem cell transplantation; AWOD, alive without disease; BEAM, BCNU, etoposide, cytrabine, melphalan; BM, bone marrow; CHOP, cyclophosphamide, pirarubicin, vendesine and dexamethasone; DHAP, dexamethasone, cytarabine and cisplatin; DHOx, dexamethasone, cytarabine and oxaliplatin; DLBCL, diffuse large B-cell lymphoma; ESHAP, etoposide, 6-methylprednisolone, cytarabine and cisplatin; FL, follicular lymphoma; HDS, high-dose sequential polychemotherapy; ICE, ifosfamide, carboplatin and etoposide; IgH, immunoglobulin heavy chain gene rearrangement; LN, lymph node; MACOP-B, Methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin; MINE, mesna, ifosfamide, mitoxantrone and etoposide; NA, not available; R, rutuximab, THP-COP, pirarubicin, cyclophosphamide, vincristine and prednisolone.

Table 3. Summary of composite lymphomas

Case No.	Diagnosis	Biopsy site	IgH	TCR	EBER-ISH	Treatment	Outcome	Ref
1	Composite DLBCL and FL	BM, spleen, LN, Retroperitoneal	NA	NA	NA	CHOP	NA	[9]
2	Composite DLBCL and FL	LN	NA	NA	NA	COP × 6+ LEM × 2+ CHOP × 1	Died, 20 m	[2]
3	Composite DLBCL and FL	LN	NA	NA	NA	NA	NA	[2]
4	Composite DLBCL and FL	LN	NA	NA	NA	CHOP, R and ABMT	Died, 24 m	[2]
5	Composite DLBCL and FL	LN	NA	NA	NA	CHOP × 6 and rituximab × 4	Died, 42 m	[2]
6	Composite DLBCL and FL	LN	+	—	—	R+ dexamethasone R+ fludarabine	Died, 11 m	case 2

ABMT, allogeneicbone marrow transplantation; AITL, angioimmunoblastic T-cell lymphoma; BM, bone marrow; CHOP, cyclophosphamide, pirarubicin, vendesine and dexamethasone; COP, pirarubicin, cyclophosphamide, vincristine and prednisone; DLBCL, diffuse large B-cell lymphoma; EBER-ISH, Epstein-Barr virus-encoded RNA in situ hybridization; FL, follicular lymphoma; IgH, immunoglobulin heavy chain gene rearrangement; LEM, liposome-entrapped mitoxantrone; LN, lymph node; NA, not available; R, rutuximab; TCR, T-cell receptor rearrangement.

individual pre- and post-transformation is a prerequisite for understanding the molecular mechanisms of the phenotypic changes in lymphoma; hence, second biopsy and analysis of clonal *IgH* and *TCR* gene rearrangements must be performed in patients with DLBCL that relapsed with enlarged lymph nodes or those with poor prognosis. Appropriate therapeutic measures must be established to improve the prognosis of these patients. Future studies must investigate a large number of this case to provide a basis for selecting the optimal therapeutic approach.

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Disclosure of conflict of interest

None.

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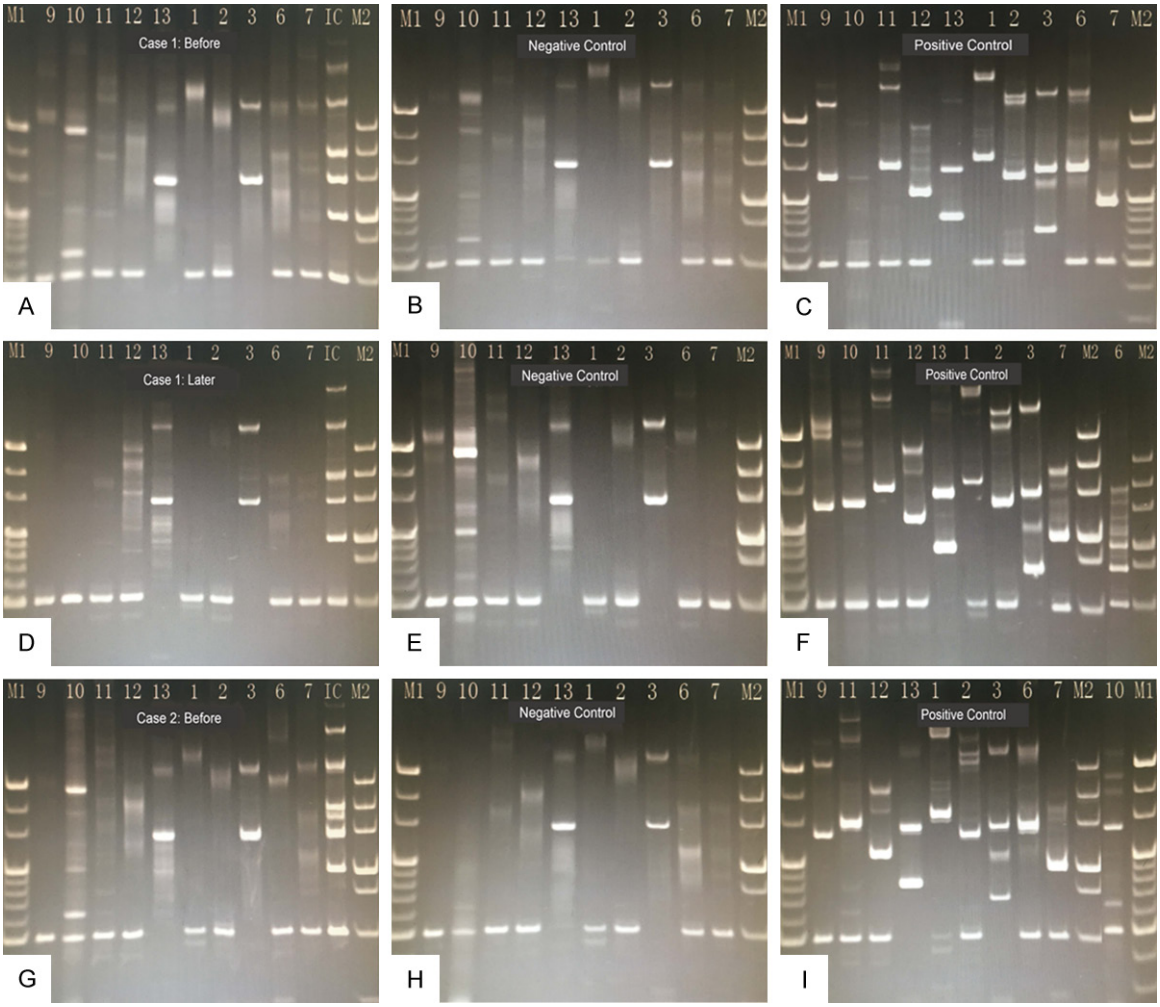
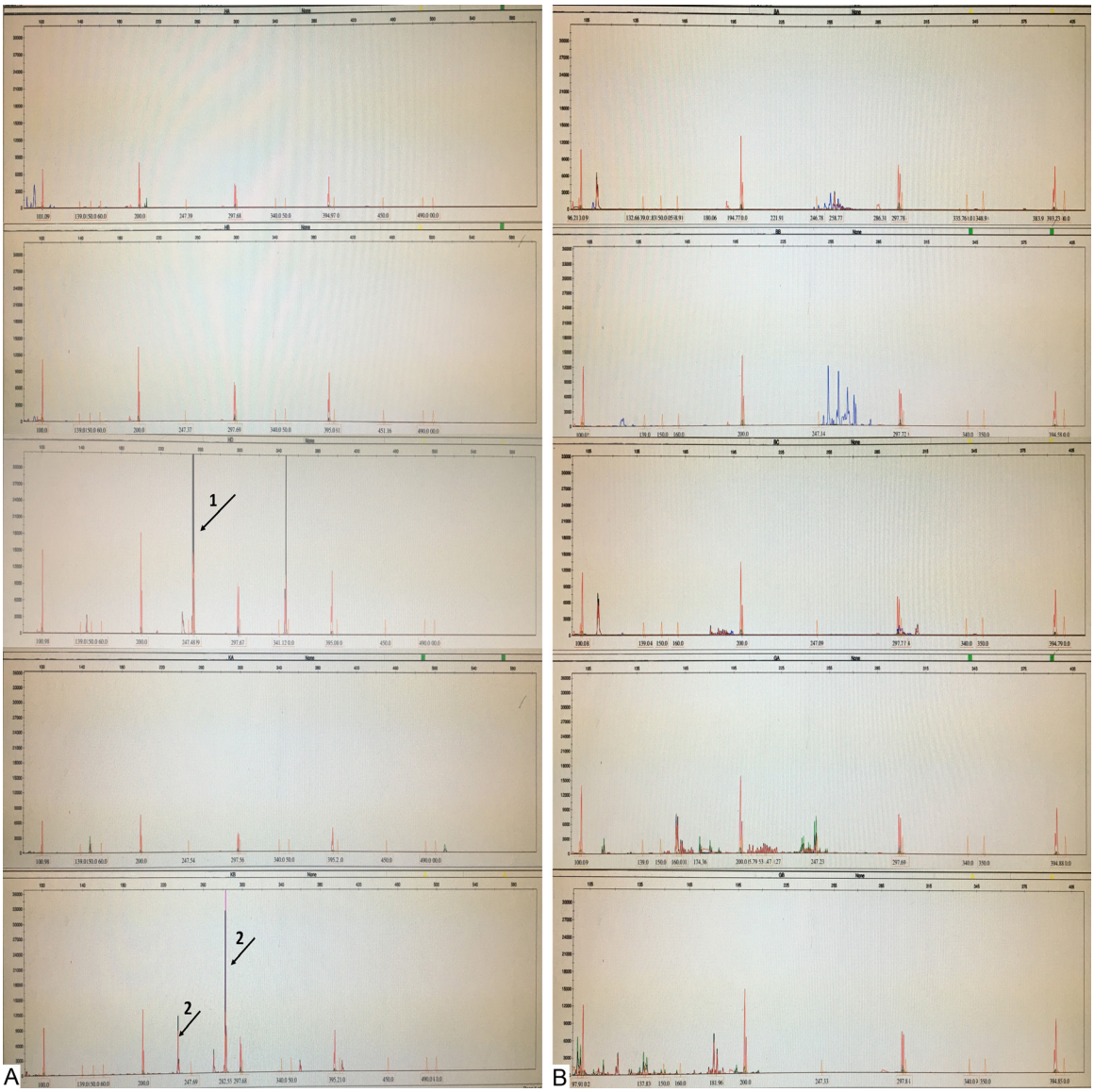


Supplementary Figure 1. Polymerase chain reaction analysis of the IgH and TCR genes of Case 1 (A-F) and Case 2 (G-I), Analysis of Polyacrylamide Gel Electrophoresis. Symbols in figures have different meanings: 1: IGH-FR1; 2: IGH-FR2; 3: IGH-FR3; 6: IGκ-VJ; 7: IGκ-V/in; 9: TCRβ-VJ1; 10: TCRβ-VJ2; 11: TCRβ-DJ; 12: TCRγ-VJ1; 13: TCRγ-VJ2; M1 & M2: Molecular weight markers; IC: Sample control. (A: Clonality analyses of patient of Case 1 when the diagnosis was DLBCL and the result revealed no clonal rearrangements. B, C: Negative control and positive control of patient of Case 1 when the diagnosis was DLBCL. D: Clonality analyses of patient of Case 1 when the diagnosis was FL and the result revealed no clonal rearrangements. E, F: Negative control and positive control of patient of Case 1 when the diagnosis was FL. G: Clonality analyses of patient of Case 2 when the diagnosis was DLBCL and the result revealed no clonal rearrangements. H, I: Negative control and positive control of patient of Case 2 when the diagnosis was DLBCL).



Supplementary Figure 2. Polymerase chain reaction analysis of the IgH and TCR genes of patient of Case 2 when the diagnosis was DLBCL and FL (A, B), Capillary Electrophoresis Gene Scanning. (A: Analyses of IGH genes with the *Arrow 1* pointing the clonal rearrangements of IGH-DH and the *Arrow 2* pointing the clonal rearrangements of IGκ-V/ in. B: Analyses of TCR genes revealed no clonal rearrangements).