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Original contribution

Non-diffuse large B-cell lymphoma transformation from follicular lymphoma: a single-institution study of 19 cases^{☆,☆☆}



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びまん性大細胞型 B 細胞リンパ腫 (DLBCL) は、濾胞性リンパ腫 (FL) の組織学的形質転換 (HT) の特徴的な組織型である。一方で non-DLBCL 型の HT は非常にまれであり、その発生率、病理組織像、および患者予後は十分に解明されていない、

今回は単一施設において、FL から non-DLBCL 型に形質転換を来した 19 症例について臨床病理学的に検索した。2000 年から 2018 年の間に FL と診断された 889 症例のうち、191 症例で HT を認めた。追跡期間中央値は 94 ヶ月であった。FL 191 例のうち 172 例 (90%) が DLBCL への転化を、残りの 19 例 (10%) は non-DLBCL 型の転化を認めた。non-DLBCL 転化症例では病理組織像に加え、免疫組織化学、フローサイトメトリー、および蛍光 in situ ハイブリダイゼーション解析を行った。Non-DLBCL 型の組織像は、古典的ホジキンリンパ腫 7 例、MYC および BCL2 再配列を伴う高悪性度 B 細胞性リンパ腫 (HGBL) 4 例、特定不能の HGBL 4 例、B 細胞性リンパ芽球性白血病/リンパ腫 2 例、未分化大細胞性リンパ腫様リンパ腫 1 例、形質芽球性リンパ腫 1 例であった。このうち 8 例について EBERish を行ったが前例陰性であった。

Non-DLBCL 型に形質転換した症例の全生存期間中央値は 13 ヶ月 (2 日~107 ヶ月の範囲) であり、19 例中 10 例 (53%) が HT で死亡した。結論として FL からの HT をきたした症例では、その治療や患者の予後の改善のために、タイムリーで正確かつ包括的な病理組織学的診断が必要である。

Table 1 Characteristics of patients with HT from FL.

Parameters	HT to non-DLBCL (n = 19)		HT to DLBCL (n = 172)	
	Synchronous FL and HT	Asynchronous, FL followed by HT	Synchronous FL and HT	Asynchronous, FL followed by HT
Number of cases (% of patients with FL)	6 (3%) ^a	13 (7%) ^b	94 (49%)	78 (41%)
Age, median (range) ^c	50 y (34–61)	60 y (45–65)	58 y (25–83)	58 y (27–84)
Sex, male (%)	4 (67%)	7 (54%)	47 (50%)	41 (53%)
Stage, III–IV (%) ^c	6 (100%)	12 (92%)	63 (67%)	57 (73%)
IPI, HI-H (%) ^c	4 (67%)	2 (15%)	27 (29%)	16 (21%)
Time between initial diagnosis of FL and HT, median (range)	NA	59 m (8–107)	NA	71 m (5–225)
Site of HT				
Lymph node	5	7	78	60
Bone marrow	1	7	4	7
Other sites	1	2	15	17
Treatment for HT				
R-CHOP ± RT	1	7	85	33
BR ± RT			1	5
R-CODOX-M/IVAC	2	3		1
Other chemotherapy ± R ± RT		2	2	33
ABVd ± R	3	1		
RT			4	1
R monotherapy				2
WW (patient's request)			2	
BSC				1
Not available				2
Response to treatment of HT				
CR	5 (83%)	8 (61%)	73 (81%)	42 (59%)
PR	1 (17%)	1 (8%)	9 (10%)	10 (14%)
SD/PD		4 (31%)	8 (9%)	19 (27%)
Not available			4	7
Stem cell transplantation	2 (33%)	3 (23%)	14 (15%)	28 (36%)
Outcome after HT, median OS	71 m	8 m	80 m	20 m

Abbreviations: ABVd, Adriamycin, bleomycin, vinblastine, and dacarbazine; BSC, best supportive care; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CODOX-M/IVAC, cyclophosphamide, vincristine, doxorubicin, and methotrexate/ifosfamide, etoposide, and cytarabine; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HI-H, high intermediate-high; HT, histological transformation; IPI, International Prognostic Index; NA, not applicable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, rituximab; RT, radiotherapy; SD, stable disease; WW, watchful waiting.

^a Three cases with both DLBCL and non-DLBCL HT were included.

^b Five cases with both DLBCL and non-DLBCL HT were included.

Table 2 Correlation between histopathological subtype and time of transformation from FL.

Histopathology of transformation	Synchronous FL and HT	Asynchronous, FL followed by HT		
		HT during WW	HT at 1st relapse	HT at ≥ 2nd relapse
Total (n = 191)	100 (52%)	16 (8%)	32 (17%)	43 (23%)
DLBCL (n = 172)	94 (49%)	12 (6%)	29 (15%)	37 (19%)
HGBL-DH (n = 4)		1	2 (1%)	1
HGBL-NOS (n = 4)	2 (1%)	1		1
CHL (n = 7)	4 (2%)	1	1	1
B-ALL (n = 2)		1		1
ALCL-like (n = 1)				1
PBL (n = 1)				1

Abbreviations: ALCL, anaplastic large-cell lymphoma; B-ALL, B-acute lymphoblastic leukemia; CHL, classic Hodgkin lymphoma; FL, follicular lymphoma; DH, double hit (with *BCL2* and *MYC* rearrangements); DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; HT, histological transformation; NOS, not otherwise specified; PBL, plasmablastic lymphoma; WW, watchful waiting.

Table 3 Morphologic findings, immunophenotypes, treatment, and outcomes of 19 patients with non-DLBCL HT from FL.

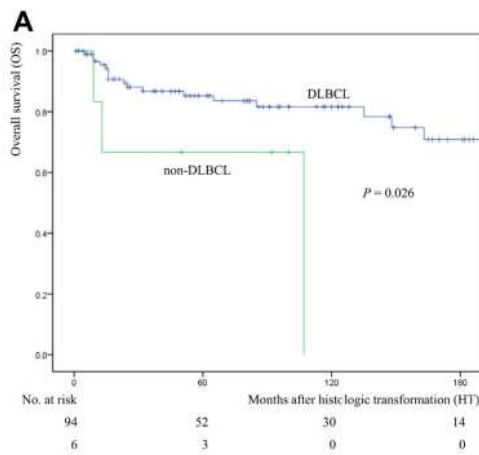
Case no.	Histology	Age/sex	IHC, positive markers	IHC, negative markers	sIg, FC	cMYC split signal	IGH/BCL2 fusion	Description of the clinical course	Outcome after HT to non-DLBCL
1	HGBL-DH	45/F	CD10, CD20, CD79a, BCL2, Ki67 index (>90%)	TdT	+	+	+	FL3a (LN), R-CHOPx6, CR, [X+16 y] FL1 (LN) and HGBL-DH (BM), EPOCH-R, CR, haplo-HSCT, [X+17 y] CD20 ⁺ DLBCL, CHASE, GEM, PD, death	DOD, 12 m
2	HGBL-DH	53/F	CD10, CD20, BCL2, Ki67 index (>90%)	TdT	NA	+	+	2018.9FL2 (LN), WW, [X+1 y] HGBL-DH (LN), R-CHOPx1, SD, R-CODOX-M/IVAC, PR, auto-HSCT	Alive, 15 m
3	HGBL-DH	60/F	CD10, CD79a, BCL2, TdT (focal)	CD20	+	+	+	FL2 (LN), R-CHOPx6, PR, R maintenancex3, PD, [X+1 y] FL1 (LN), B, CHASE, R-EPOCH, SD, clinical trial, [X+3 y] HGBL-DH (BM), EPOCHx3, HGBL in CR and FL1 in SD, allo-HSCT, CR	Alive, 21 m
4	HGBL-DH	65/M	CD10, CD20, CD79a, BCL2, Ki67 index (70%)	TdT	+	+	+	FL3a (LN), WW (patient request), [X+4 y] DLBCL (LN), R-CHOPx6, CR, [X+5 y] HGBL-DH (LN), CHASER, GDP, EPOCH, PD	DOD, 4 m
5	HGBL-NOS	56/M	CD10, CD20, CD79a, BCL2, Ki67 index (80%)	CD3, CD5, CD30, TdT	+	+	NA	HGBL-NOS and FL1 (LN, BM, and intestine), R-CODOX-M/IVAC, PR, [X+6 m] HGBL (ileum), R-ESHAP, PD, death	DOD, 13 m
6	HGBL-NOS	34/F	CD10, CD20, BCL2, BCL6, MUM1, Ki67 index (80%)	CD3, CD5, TdT	NA	—	+	HGBL-NOS and FL1 (LN), DLBCL and FL3a (terminal ileum), and FL2 (rectum), R-CODOX-M/IVAC, CR, [X+2 y] FL2 (LN), Rx7, CR, R maintenancex8	Alive, 50 m
7	HGBL-NOS	48/M	CD10, CD20, BCL2, Ki67 index (90%)	CD3, TdT	—	—	+	FL2 (LN), WW (LTB), [X+7 m] HGBL-NOS (BM), R-CHOPx8, CR, R maintenancex12	Alive, 46 m
8	HGBL-NOS	65/M	CD10, CD20, Ki67 index (90%)	CD3, TdT	+	DJ	DJ	FL2 (LN), multiple chemotherapies, [X+8 y] HGBL-NOS (BM) and DLBCL (LN)	DOD, 2 m
9	CHL-MC	45/F	CD15, CD20 (focal), CD30, PAX5	CD3, CD10, CD45, ALK, EBER1	NA	NA	DJ	FL1 (LN), R-CHOP, persistent fever, CHL-MC (BM), continue of R-CHOP, PD, ABVdx2, PD, R-ESHAPx3, auto-HSCT, R-ESHAP, PD, CHL (BM), ICE, C-MOPP, B, death	DOD, 10 m
10	CHL-MC	50/M	CD30, PAX5	CD3, CD15, CD20, CD45, ALK, EBER1	NA	NA	+	CHL-MC (LN) and FL1 (duodenum), R-ABVdx8, CR, [X+2 y] FL1 (duodenum), WW, [X+6 y] DLBCL (LN), R-ESHAPx4, CR, auto-HSCT, CR	Alive, 100 m
11	CHL-MC	50/M	CD15, CD30, PAX5	CD3, CD20, CD45, ALK, EBER1	NA	NA	+	CHL-MC (LN) and FL1 (BM), R-ABVdx8, CR, [X+4 y] CHL (LN), ESHAPx3, CR, allo-HSCT, CR	Alive, 92 m
12	CHL-MC	60/F	CD30, PAX5	CD10, CD20, CD79a, EBER1	NA	NA	DJ	FL2 (LN), R-CHOPx6, CR, [X+6y] DLBCL (LN), BRx4, CR, [X+8 y] FL1 (LN), R monotherapy, C-MOPPx6, PR, [X+10 y] CHL-MC (LN), BV	Alive, 5 m
13	CHL-MC	61/M	CD15, CD20 (focal), CD30, PAX5	CD3, ALK, EBER1	NA	NA	—	CHL-MC (LN, IGH/BCL2 ⁺) and FL1 (duodenum, IGH/BCL2 ⁺), ABVdx8, CR, [X+7y] FL2 (LN), BRx6, PD, [X+8 y] DLBCL (LN), R-ICE, clinical trial, R-GDP, death	DOD, 107 m

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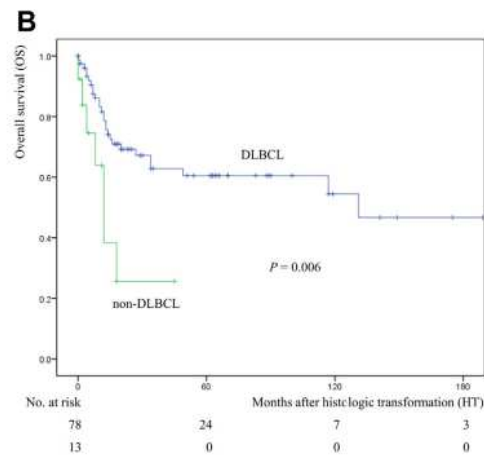
14	CHL-MC	61/F	CD15, CD20 (focal), CD30, PAX5	CD3, CD10, CD45, ALK, BCL2, EBER1	NA	NA	+	DLBCL and FL3a (LN), R-CHOPx8, CR, [X+1 y] CHL-MC (LN), RT, DLBCL (lung), EPOCH, PD, death	DOD, 8 m
15	CHL-LR	61/M	CD30, PAX5	CD3, CD10, CD15, CD20, BCL2, EBER1	NA	NA	DJ	FL3a (<i>IGH/BCL2</i> ⁺) and MZL (<i>IGH/BCL2</i>) (skin), WW, [X+2 y] CHL-LR and FL1 (LN), ABVdx2+RT, CR	Alive, 15 m
16	B-ALL (DH)	53/M	TdT, CD10, CD20 (focal), CD79a (focal), BCL2, Ki67 index (>90%)		-	+	+	FL3a (LN), WW, [X+7 y] B-ALL (BM, LN, and skin), LSG16 regimen for ALL+R, PD, IVAC, GDP, death	DOD, 4 m
17	B-ALL (DH)	60/M	CD10, CD20 (focal), CD79a, Ki67 index (>90%)	TdT	+	+	+	FL2 (LN), R-CHOPx6, CR, [X+2 y] FR, CR, [X+5 y] B-ALL (BM), ALL2020 regimen, PD, IVAC, GEM, DEX, death	DOD, 12 m
18	ALCL-like	63/M	CD45, CD45RO	CD3, CD5, CD7, CD10, CD15, CD20, CD30, CD34, CD56, CD79a, ALK, BCL2, BCL6, granzyme B, MPO, MUM1, PAX5, TIA1, TdT	NA	NA	+	FL, C-MOPPx4, CR, [X+1 y] FL, VP-16, CR, [X+7 y] FL2 (LN), R-C-MOPPx6, CR, [X+11 y] ALCL-like (liver), ICE	Alive, 13 m
19	PBL	53/F	CD30, CD38, CD45, CD138, BCL2, MUM1, PAX5, CD45, λ	CD3, CD5, CD10, CD20, CD34, CD79a, CD117, ALK, MPO, TdT, κ, EBER1	NA	NA	+	FL2 (LN and BM), R-CHOPx6, CR, WW, R monotherapy, CR, [X+5 y] FL2 (BM), C-MOPP, B, PR, [X+7 y] FL1 (BM), GEM, PD, PBL (BM), death	DOD, 2 d

Bold signifies main diagnosis. Abbreviations: ABVd, Adriamycin, bleomycin, vinblastine, and dacarbazine; ALCL, anaplastic large-cell lymphoma; B, bendamustine; B-ALL, B-acute lymphoblastic leukemia (B-cell lymphoblastic leukemia/lymphoma); BM, bone marrow; BV, brentuximab vedotin; CHASE, cyclophosphamide, cytarabine, etoposide, and dexamethasone; CHL, classic Hodgkin lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; C-MOPP, cyclophosphamide, vincristine, prednisone, and procarbazine; CODOX-M/IVAC, cyclophosphamide, vincristine, doxorubicin, and methotrexate/ifosfamide, etoposide, and cytarabine; CR, complete response; DEX, dexamethasone; DJ, difficult to judge; DH, double hit (with *BCL2* and *MYC* rearrangements); DLBCL, diffuse large B-cell lymphoma; DOD, dead of disease; EPOCH, etoposide, vincristine, Adriamycin, cyclophosphamide, and prednisone; ESHAP, etoposide, methylprednisone, cytarabine, and cisplatin; FC, flow cytometry; FL, follicular lymphoma; FR, fludarabine and rituximab; GDP, gemcitabine, cisplatin, and dexamethasone; GEM, gemcitabine; HGBL, high-grade B-cell lymphoma; HSCT, hematopoietic stem cell transplantation; HT, histological transformation; ICE, ifosfamide, carboplatin, and etoposide; LN, lymph node; LR, lymphocyte rich; LTB, low tumor burden; MC, mixed cellularity; MZL, marginal zone lymphoma; NA, not available; NOS, not otherwise specified; PBL, plasmablastic lymphoma; PD, progressive disease; PR, partial response; R, rituximab; RT, radiotherapy; SD, stable disease; slg, surface immunoglobulin; WW, watchful waiting.

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synchronous DLBCL vs. non-DLBCL



asynchronous DLBCL vs. non-DLBCL

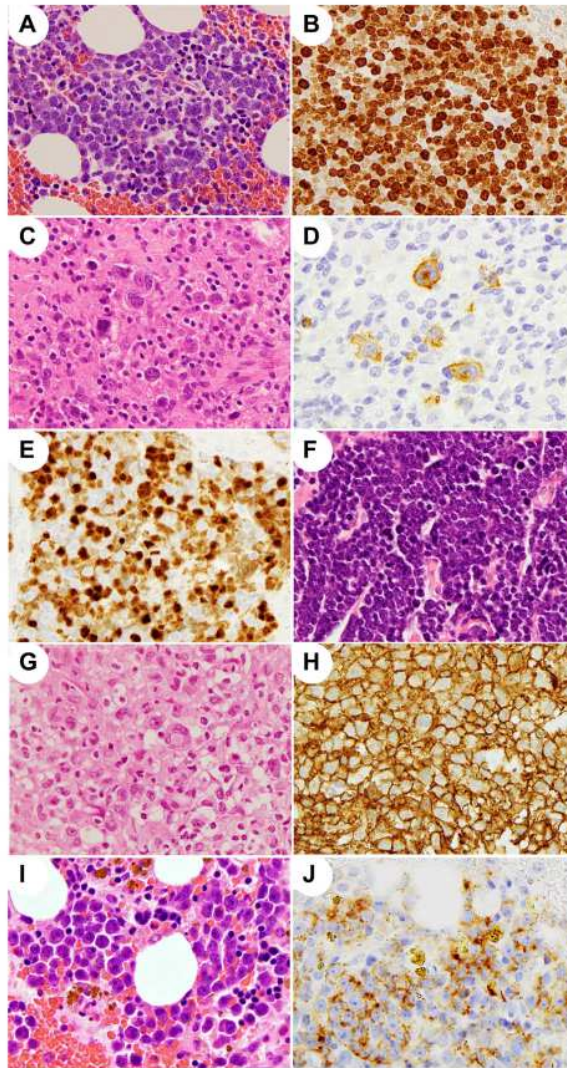


Fig. 1 Histopathological assessment of patient tissue. High-grade B-cell lymphoma (double hit) in the bone marrow of case no. 1 (A, H&E, x 400; B, Ki67, x 400). Classic Hodgkin lymphoma in the lymph node of case no. 10 (C, H&E, x 400; D, CD30, x 400). B-acute lymphoblastic leukemia in the lymph node of case no. 16 (E, TdT, x 400) and in the bone marrow of case no. 17 (F, H&E, x 400). Anaplastic large-cell lymphoma-like lymphoma in the liver of case no. 18 (G, H&E, x 400; H, CD45RO x 400). Plasmablastic lymphoma in the bone marrow of case no. 19 (I, H&E, x 400; J, CD138 x 400). H&E, hematoxylin and eosin