Good prognosis for follicular lymphoma with estrogen receptor α-positive follicular dendritic cells

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Abstract
Follicular lymphoma (FL) has a meshwork of follicular dendritic cells (FDCs). We previously demonstrated the presence of estrogen receptor alpha (ERα)+CD23+ FDCs in grades 1-2 FL. The significance of FDCs as a prognostic factor in FL remains unknown. The current study aimed to compare clinicopathological features, including prognosis, between FL with and without ERα+ FDCs. This study evaluated the clinicopathological significance of ERα expression in 70 FL patients by immunostaining. The presence of ERα mRNA on FDCs from 5 FL patients was confirmed by CD21/ERα double staining (immunohistochemistry and in situ hybridization). We defined patients with frequent ERα expression as the ERαhigh group and those with infrequent ERα expression as the ERαlow group. Thirty-two patients were assigned to the ERαhigh group (45.7%), and 38 patients were assigned to the ERαlow group (54.3%). Both overall survival (OS) and progression-free survival (PFS) were significantly better in the ERαhigh group than in the ERαlow group (OS, log-rank, P = .0465; PFS, log-rank, P = .0336). Moreover, high ERα expression on FDCs was an independent prognostic factor for OS in both the univariate (hazard ratio [HR] 0.163; P = .0260) and multivariate (HR 0.050; P = .0188) analyses and for PFS in both the univariate (HR 0.232; P = .0213) and multivariate (HR 0.084; P = .0243) analyses. ERα mRNA expression was detected in CD21+ FDCs within the neoplastic follicles of FL patients. In conclusion, a neoplastic follicular microenvironment with ERα-positive FDCs might affect the grade and presence of the follicular pattern of FL and improve patient prognosis.

KEYWORDS
estrogen receptor alpha, follicular dendritic cell, follicular lymphoma, FLIPI, Prognosis

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INTRODUCTION

Follicular lymphoma (FL) is a germinal center (GC)-derived lymphoma\(^1,2\) that is frequently followed by an indolent clinical course.\(^3,4\) As prognostic factors, the Follicular Lymphoma International Prognostic Index (FLIPI)\(^5\) and FLIPI2\(^6\) are commonly used. Recently, m7-FLIPI,\(^7\) which includes the mutation status of 7 genes, and progression of disease within 2 years (POD24 or POD2),\(^8\) which is defined as relapse or progression of FL within 24 months (2 years) after diagnosis, have been used as prognostic factors. In addition, various proteins of neoplastic cells themselves, such as CD5,\(^9\) GNA13,\(^10\) and FOXP-1,\(^11\) are considered prognostic factors. In the microenvironment, it is unclear whether tumor-associated macrophages and programmed cell death-1\(^+\) cell infiltration are associated with prognosis.\(^12,13\) Concerning follicular dendritic cells (FDCs), a tight CD21\(^+\) FDC meshwork frequently promotes transformation into large B-cell lymphoma,\(^3\) although the extent of Ki-M4p\(^+\) or the CD23\(^+\) FDC meshwork is not associated with treatment outcome or survival time.\(^14\)

We previously demonstrated that the number of ER\(^\alpha\) cells was positively correlated with the width of the CD23\(^+\) FDC meshwork in both nonneoplastic GC and neoplastic follicle, and that estrogen receptor alpha (ER\(^\alpha\)) CD23\(^+\) FDCs supported the neoplastic follicular microenvironment of grades 1-2 (G1-2) FL, but not G3 FL, suggesting the possibility of the usefulness of antiestrogen therapy against FL.\(^15\)

This study first compared clinicopathological features and prognosis between FL patients with more and less frequent ER\(^\alpha\) FDCs and investigated the significance of ER\(^\alpha\) FDCs in the FL microenvironment.

MATERIALS AND METHODS

2.1 Patients and samples

We investigated 70 tissue samples from FL patients before treatment. Pathological diagnoses were determined at Yamagata University Hospital and Yonezawa City Hospital in Japan and Harbin Medical University Cancer Hospital in China between 2003 and 2018 using the rituximab-containing regimen. Specific FL variants and subtypes, including testicular FL, in situ FL, duodenal-type FL, pediatric-type FL, and primary cutaneous follicle center lymphoma, were excluded from this study. The FL specimens were classified as G1-2 (n = 35), G3A (n = 22), or G3B (n = 13) in accordance with the WHO Classification Revised Fourth Edition.\(^16\) The histological pattern of these cases was classified as follicular pattern (n = 52) and another pattern (n = 18).\(^16\) Tissues were fixed in 10% neutral-buffered formalin for 6 to 12 hours at room temperature, embedded in paraffin (formalin-fixed paraffin-embedded; FFPE), and used for hematoxylin-eosin staining, immunostaining (IHC), and in situ hybridization (ISH). This study was approved by the Research Ethics Committee of Yamagata University Faculty of Medicine (H29-343 & 2019-108) and the Research Ethics Committee of Harbin Medical University Cancer Hospital (KY2016-25) and was performed in accordance with the Declaration of Helsinki.

2.2 Evaluation of ER\(^\alpha\) IHC

IHC was performed as previously described,\(^17\) and a specific antibody for ER\(^\alpha\) (EP1; rabbit IgG, Dako, Agilent Technologies, Santa Clara, California) was used. IHC was performed using an Autostainer Link 48 system (Agilent Technologies). ER\(^\alpha\) reactivity was estimated as previously described.\(^15\) Briefly, cells positive for ER\(^\alpha\) were counted in five neoplastic follicles for each case. In FL specimens with diffuse proliferation, positive reactions were counted in five high-power fields (HPFs) at the area of diffuse proliferation. [Modified]: We revised the mean value of the number of ER\(^\alpha\)-positive cells/HPF (ER\(^\alpha\)/HPF, 40x magnification, 0.159 mm\(^2\)), which referred to the histological grading of the WHO Classification Revised Fourth Edition\(^16\) as follows: ER\(^\alpha\)/HPF = mean value of the number of ER\(^\alpha\) cells/area of neoplastic follicles (mm\(^2\)) × 0.159 mm\(^2\) (×40 magnification). Our previous study demonstrated that the number of ER\(^\alpha\) was substitutable as a width of CD23\(^+\) FDC meshwork in nonneoplastic and neoplastic follicles, and indicated that the majority of ER\(^\alpha\) FDCs simultaneously expressed CD23.\(^15\) Therefore, we estimated ER\(^\alpha\)/HPF as a semi-quantitative marker of the width of ER\(^\alpha\) CD23\(^+\) FDC meshwork in this study.

2.3 IHC of other proteins

To confirm the immunophenotype of FL, IHC was performed using antibodies specific for CD10 (56C6; mouse IgG1, Dako, Agilent Technologies, Santa Clara, California), CD20 (L26; IgG2a, Dako, Agilent Technologies, Dako, Agilent Technologies), BCL2 (124; mouse IgG1, Dako, Agilent Technologies), BCL2 (E17; rabbit IgG, Abcam, Cambridge, UK), BCL6 (PG-B6p; mouse IgG1, Dako, Agilent Technologies), MUM1 (MUM1p; mouse IgG1, Dako, Agilent Technologies), CD21 (1F8; IgG1, Dako, Agilent Technologies), CD23 (DAK-CD23; mouse IgG1, Dako, Agilent Technologies), and CD23 (SP23; rabbit IgG, Nichirei, Tokyo, Japan) by using an Autostainer Link 48 system (DAKO, Agilent Technologies). The reactivity of CD10, CD20, BCL2, BCL6, and MUM1 was considered positive if more than 30% of the neoplastic cells were positive. The area of the neoplastic follicle was determined from images and estimated as the gross area by ImageJ as previously described.\(^15,18,19\) The CD23\(^+\) FDC pattern was divided into 2 groups: none/dim or focal/marginal/diffuse.

2.4 Double staining (IHC and ISH) of serial sections

To identify ER\(^\alpha\)-expressing cells, double staining (IHC/ISH) was performed using the FFPE serial sections of the 5 FL patients with only follicular pattern and the 5 FL patients with diffuse pattern, and one uterine endometrioid carcinoma patient (as a positive control) as previously described.\(^20\) with minor modifications. Briefly, in one section, CD21 immunostaining was performed using an Autostainer Link 48 system (Dako, Agilent Technologies) and visualized with 3,3’-diaminobenzidine. For the ISH of other sections, digoxigenin-labelled
riboprobes encoding human ERα (human estrogen receptor 1, 854 bp, nucleotides 3001-3845) and an ISH kit (Genostaff, Tokyo, Japan) were used. Probes were hybridized for 24 hours at 60°C, incubated with anti-digoxigenin-alkaline phosphatase (Roche Diagnostics, Indianapolis, Indiana) for 1 hour at room temperature, and visualized with BCIP/NBT Substrate System (DAKO, Agilent Technologies) for 24 hours at room temperature. The visual images for CD21 IHC and ERα ISH were overlaid by using ImageJ. Sense probes were used as negative controls. Nuclear staining was performed with Kernechtrot.

2.5 | Statistical analysis

To compare the clinicopathological characteristics of FL, the χ² test, Fisher's exact test or the Mann-Whitney test was used. The endpoint of overall survival (OS) was defined as the time from diagnosis until all-cause death, and the endpoint of progression-free survival (PFS) was defined as the time from diagnosis until relapse due to FL. Kaplan-Meier curves of OS and PFS were drawn and compared by the log-rank test. To propose prognostic factors, univariate and multivariate Cox proportional hazards regression models were used. Statistical analyses were performed using JMP version 14 (SAS Institute, Tokyo, Japan). Differences with P values <.05 were considered significant in each analysis.

3 | RESULTS

3.1 | IHC and ISH analyses of ERα

In the IHC analysis, ERα expression was detected mainly in FDCs in neoplastic follicles, as previously reported. OS, PFS, and ERα/HPF were compared between the ERα high-expression (ERα\textsuperscript{high}) and ERα low-expression (ERα\textsuperscript{low}) groups. As a result, most of the significant differences in OS and PFS were observed when FL patients were divided into 2 groups: ≥ 3 ERα/HPF and <3 ERα/HPF. Therefore, patients with ≥3 ERα/HPF were assigned to the ERα\textsuperscript{high} group, and the other patients were assigned to the ERα\textsuperscript{low} group (<3 ERα/HPF). Thirty-two patients (32/70, 45.7%) were assigned to the ERα\textsuperscript{high} group, and 38 patients (38/70, 54.3%) were assigned to the ERα\textsuperscript{low} group. ERα/HPF were 10.2 ± 6.45 in the ERα\textsuperscript{high} group and 0.20 ± 0.54 in the ERα\textsuperscript{low} group (P < .0001). In sequential IHC/ISH, the expression of ERα mRNA was detected in FDCs within the neoplastic follicles of 5 FL patients (Figure 1b,c). ERα mRNA was not detected in diffuse proliferation area of 5 FL patients (Figure 1d) and CD21+ FDC meshwork hardly/did not exist in this area.

3.2 | Relationship between the frequency of ERα expression and the clinicopathologic features of FL

The comparison of each clinicopathological feature between the ERα\textsuperscript{high} and ERα\textsuperscript{low} groups is shown in Table 1. Regarding the histological grade, there was more G1-2 FL in the ERα\textsuperscript{high} group than in the ERα\textsuperscript{low} group and more G3 FL in the ERα\textsuperscript{low} group than in the ERα\textsuperscript{high} group (P < .0001). Moreover, the ERα\textsuperscript{high} group had a higher frequency of the follicular proliferative pattern than the ERα\textsuperscript{low} group (P < .0001). Immunohistochemically, the ERα\textsuperscript{high} group had a higher

![Image of follicular lymphoma](image_url)
frequency of the CD23⁺ FDC meshwork than the ERα<sub>low</sub> group (P < .0001). In the initial therapy, there was a more watchful wait in the ERα<sub>high</sub> group than in the ERα<sub>low</sub> group (P = .0077). However, other features, such as age, sex, FLIPI, t(14;18)(q32;q21), the expression of other markers (CD10, BCL2, BCL6, and MUM1), the initial therapy regimen, and the rate of complete response to initial therapy were not significantly different between the ERα<sub>high</sub> and ERα<sub>low</sub> groups.

### 3.3 Comparison of survival between the ERα<sub>high</sub> and ERα<sub>low</sub> groups

Kaplan-Meier curves of OS and PFS are shown in Figure 2. The ERα<sub>high</sub> group had a significantly better prognosis for both OS and PFS than the ERα<sub>low</sub> group (OS, log-rank, P = .0465; PFS, log-rank, P = .0336).

**TABLE 1** ERα expression on follicular dendritic cell (FDC) in follicular lymphoma (70 cases)

| Clinical features                          | ERα/HPF ≥ 3 (n/N [%]) | Positive cases (N = 32) | Negative cases (N = 38) | P value |
|--------------------------------------------|-----------------------|-------------------------|-------------------------|---------|
| Age (median [range]) (years)               |                       | 58 (40-82)              | 60 (38-80)              | .2289<sup>a</sup> |
| Age >60 y                                  |                       | 12/32 (37.5)            | 18/38 (47.4)            | .4051   |
| Male/female                                |                       | 13/19                   | 19/19                   | .4328   |
| Ann Arbor stage III-IV                     |                       | 17/31 (54.8)            | 19/34 (55.9)            | .9326   |
| Bulky mass > 6 cm                          |                       | 6/31 (19.4)             | 4/34 (11.8)             | .6150   |
| Lymph node > 4 regions                     |                       | 14/31 (45.2)            | 13/34 (38.2)            | .5714   |
| Bone marrow involvement                    |                       | 8/24 (33.3)             | 5/31 (16.1)             | .1364   |
| Hemoglobin level < 12 mg/dL                |                       | 8/31 (25.8)             | 9/34 (26.5)             | .9515   |
| Evaluated LDH level                        |                       | 11/31 (35.5)            | 19/34 (55.9)            | .0994   |
| β2-microglobulin                           |                       | 14/21 (66.7)            | 17/22 (77.3)            | .4383   |
| FLIPI, high risk                           |                       | 12/31 (38.7)            | 13/34 (38.2)            | .9687   |
| t(14;18)(q32;q21)                           |                       | 14/20 (70.0)            | 6/10 (60.0)             | .8911   |
| Histological features                      |                       |                        |                        |         |
| Grade 1–2 (baseline G3A & 3B)              |                       | 30/32 (93.8)            | 5/38 (13.2)             | <.0001<sup>b</sup> |
| Follicular pattern (baseline including diffuse pattern) | | 31/32 (96.9) | 21/38 (55.3) | <.0001<sup>b</sup> |
| Immunohistochemistry                        |                       |                        |                        |         |
| CD10 expression                            |                       | 28/32 (87.5)            | 32/38 (84.2)            | .7452   |
| BCL2 expression                            |                       | 32/32 (100)             | 33/38 (86.8)            | .0581<sup>b</sup> |
| BCL6 expression                            |                       | 29/32 (90.6)            | 30/38 (79.0)            | .2083   |
| MUM1 expression                            |                       | 4/32 (12.5)             | 12/38 (31.6)            | .1078   |
| CD23 FDC pattern (baseline dim/none)       |                       | 27/32 (84.4)            | 9/37 (24.3)             | <.0001  |
| Initial therapy                            |                       |                        |                        |         |
| Watchful wait                              |                       | 9/32 (28.2)             | 3/35 (8.57)             | .0077<sup>b</sup> |
| Chemotherapy                               |                       |                        |                        |         |
| R-containing regimen                       |                       | 23/32 (71.9)            | 28/35 (80.0)            | .3319   |
| Others                                     |                       | 0/32 (0)                | 1/35 (2.86)             | 1<sup>b</sup> |
| Radiation therapy                          |                       | 0/32 (0)                | 2/35 (5.71)             | .4934<sup>b</sup> |
| Chemotherapy & radiation therapy           |                       | 0/32 (0)                | 1/35 (2.86)             | 1<sup>b</sup> |
| Others                                     |                       | 0/32 (0)                | 0/35 (0)                | NA      |
| Complete response to initial therapy       |                       | 16/23 (69.6)            | 26/33 (78.8)            | .6380   |
| Median follow up (median [range]) (months) |                       | 32 (7-85)               | 57 (10-137)             |         |

Abbreviations: FLIPI, follicular lymphoma international prognostic index; HPF, high-power field (×40 magnification, 0.159 mm²); LDH, lactate dehydrogenase; NA, not available; R, rituximab.

<sup>a</sup>Mann-Whitney test.

<sup>b</sup>Fisher exact test.
3.4 | Univariate and multivariate analyses of OS and PFS

The results of the univariate and multivariate analyses of OS are shown in Table 2. In the univariate analysis, age (≥61; hazard ratio (HR), 6.520 [95% confidence interval (CI) [1.814-23.44]], P = .0011), Ann Arbor stage III-IV (HR, 15.32 [95% CI, [1.971-119.0]], P = .0003), high serum LDH (HR, 4.264 [95% CI [1.205-20.17]], P = .0235), number of lymphadenopathy areas (≥4; HR, 4.601 [95% CI [1.443-17.30]], P = .0098), hemoglobin (<12 g/dL; HR, 4.497 [95% CI [1.396-14.49]], P = .0131), high-risk FLIPI (HR 8.743 [95% CI [2.585-39.65]], P = .0004), CD10 positivity (HR, 0.178 [95% CI [0.053-0.623]], P = .0086), and ERα/HPF (≥3; HR, 0.163 [95% CI [0.009-0.834]], P = .0260) were significantly associated with OS. Moreover, in the multivariate analysis, high-risk FLIPI was an independent poor prognostic factor for OS (HR, 15.63 [95% CI [3.579-102.4]], P < .0001), and ERα/HPF were an independent good prognostic factor for OS (HR, 0.050 [95% CI [0.002-0.606]], P = .0188).

The results of the univariate and multivariate analyses of PFS are also shown in Table 2. In the univariate analysis, age (HR, 4.850 [95% CI [1.805-15.24]], P = .0015), Ann Arbor stage III-IV (HR, 10.33 [95% CI [2.876-65.90]], P < .0001), number of lymphadenopathy areas (HR, 5.981 [95% CI [2.153-19.14]], P = .0006), high-risk FLIPI (HR, 9.157 [95% CI [3.156-33.00]], P < .0001), follicular pattern (another pattern, including the diffuse pattern, at baseline) (HR, 0.328 [95% CI [0.127-0.848]], P = .0222), and ERα/HPF (HR, 0.232 [95% CI [0.037-0.825]], P = .0213) were significantly associated with PFS. Moreover, in the multivariate analysis, high-risk FLIPI was an independent poor prognostic factor for PFS (HR, 11.00 [95% CI [3.319-46.61]], P < .0001), and ERα/HPF were an independent good prognostic factor for PFS (HR, 0.084 [95% CI [0.009-0.708]], P = .0243).

4 | DISCUSSION

There was a higher frequency of G1-2 FL, the follicular pattern and CD23+ FDCs in the ERαhigh group than in the ERαlow group in this study (Table 1). The FDC immunophenotype of G1 FL resembles that of the light zone (LZ). We previously described that ERα CD23+ FDCs were distributed both in the LZ of GC and in the neoplastic follicle from G1-2 FL, unlike G3 FL, indicating that the microenvironment of the ERαhigh group is similar to the LZ of GC supported by ERα CD23+ FDCs.

To the best of our knowledge, this study was the first to reveal an association between high ERα expression and a good prognosis in FL. Established prognostic factors, including FLIPI and FLIPI2, are used to judge the pre-treatment status. Two additional prognostic factors were recently reported: m7-FLIPI is used to determine the pre-treatment status, and minimal residual disease and POD24 are used to determine the post-treatment status. However, their roles as prognostic factors in different histological grades, except for G3B, have become questionable during current therapies. Immunohistochemical expression of CD5, QNA-13, and FOXP-1 was recently reported as another prognostic factor of FL. The roles of intrafollicular tumor-associated macrophages and programmed cell death-1 expression as prognostic factors have not yet been established. In particular, the extent of the FDC meshwork is not associated with OS and could be either a good or poor prognostic factor of transformation. These results suggest that the relation between FDCs and prognosis remains ambiguous. However, we first described frequent ERα expression on FDCs in FL as an independent good prognostic factor in FL patients. Our results suggest that high ERα expression might be a candidate prognostic factor for FL. Moreover, ERα/HPF can be counted in the same field that pathologists usually examine to judge the histological grade of FL. Furthermore, ERα expression can be easily estimated with IHC because it is used worldwide for breast cancer hormone therapy.

The role of ERα expression on FDCs in FL and how hormone therapy can be applied for FL should be investigated in the future. We previously suggested that hormone therapy tended to decrease ERα expression and the CD21+ CD23+ FDC meshwork in non-neoplastic axillary lymph nodes. Tamoxifen, an ERα antagonist, regulates both non-neoplastic and malignant hematopoietic cells and promotes the apoptosis-inducing effect of ceramide for leukemia and other
| Parameter | Overall survival | | Progression-free survival | |
| --- | --- | --- | --- | --- |
| | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Age ≥ 61 (years) | 6.520 (1.814-23.44) | .0011 | 4.850 (1.805-15.24) | .0015 |
| Sex: male (baseline female) | 2.194 (0.744-6.466) | .1418 | 2.072 (0.815-5.636) | .1260 |
| Ann Arbor, stage III-IV (baseline I-II) | 15.32 (1.971-119.0) | .0003 | 10.33 (2.876-65.90) | <.0001 |
| High serum LDH (baseline standard value) | 4.264 (1.205-20.17) | .0235 | 2.330 (0.836-7.503) | .1075 |
| Number of lymphadenopathy areas >4 | 4.601 (1.443-17.30) | .0098 | 5.981 (2.153-19.14) | .0006 |
| Bulky mass > 6 cm | 0.645 (0.035-3.344) | .6565 | 1.279 (0.199-4.667) | .7541 |
| Bone marrow involvement | 1.617 (0.351-5.554) | .4971 | 2.146 (0.590-6.270) | .2231 |
| Hemoglobin <12 g/dL | 4.497 (1.396-14.49) | .0131 | 2.464 (0.832-6.670) | .0991 |
| FLIPI, high-risk (baseline low-intermediate risk) | 8.743 (2.585-39.65) | .0004 | 15.63 (3.579-102.4) | <.0001 |
| CD10 positivity | 0.178 (0.053-0.623) | .0086 | 0.334 (0.125-1.094) | .0685 |
| BCL2 positivity | 0.547 (0.146-3.535) | .4643 | 0.844 (0.239-5.347) | .8253 |
| BCL6 positivity | 2.425 (0.621-16.27) | .2224 | 0.760 (0.283-2.400) | .615 |
| MUM1 positivity | 3.191 (0.981-10.47) | .0536 | 1.581 (0.541-4.198) | .3828 |
| Histological grade 3A & 3B (baseline grade 1-2) | 1.744 (0.582-6.365) | .3311 | 3.351 (0.410-24.10) | .2386 |
| Follicular pattern (baseline another pattern including diffuse pattern) | 0.434 (0.143-1.355) | .1451 | 1.877 (0.461-7.568) | .3684 |
| CD23 FDC marginal and diffuse pattern (baseline none and dim pattern) | 1.007 (0.342-2.969) | .9890 | 0.759 (0.275-1.984) | .5751 |
| ERα/HPF ≥ 3 | 0.163 (0.009-0.834) | .0260 | 0.050 (0.002-0.606) | .0188 |

Abbreviations: CI, confidence interval; ERα, estrogen receptor alpha; FDC, follicular dendritic cell; FLIPI, follicular lymphoma international prognostic index; HPF, high-power field (×40 magnification, 0.159 mm²); HR, hazard ratio; LDH, lactate dehydrogenase.
cancers. Furthermore, tamoxifen is also considered a G protein-coupled estrogen receptor (GPER) agonist and suppresses the proliferation of Jurkat cells, a T-ALL cell line expressing GPER. GPER promotes the survival of mantle cell lymphoma cells. Therefore, our results suggest that GC-derived lymphomas, including FL, might be driven by apoptosis via the application of tamoxifen because FDCs prevent FL cells against apoptosis. We should investigate GPER expression on lymphomas accompanied by the FDC meshwork in a further study.

We acknowledge several limitations of this study. First, it is necessary that future studies carefully evaluate the significance of ERα+ FDCs. For instance, pER (Ser118), as a predictive marker of a good response to tamoxifen, can be analyzed on FDCs in FL to more effectively adapt anti-hormone therapy. Second, it is important to investigate ERα+ FDCs in other GC-derived lymphomas, such as angioimmunoblastic T-cell lymphoma, classic Hodgkin lymphoma, and nodular lymphocyte predominant Hodgkin lymphoma.

In conclusion, this study is the first to demonstrate the different clinicopathological characteristics between ERα+high and ERα+low patients with FL. These results suggest that a neoplastic follicular microenvironment with ERα-positive FDCs might affect the histological grade and presence of the follicular pattern of FL and indicate a good prognosis for FL patients.

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CONFLICT OF INTEREST
All authors declare no conflict of interest.

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