Recurrent loss of heterozygosity in 1p36 associated with *TNFRSF14* mutations in *IRF4* translocation negative pediatric follicular lymphomas

Idoia Martin-Guerrero,[1,2]* Itziar Salaverria,[1]* Birgit Burkhardt,[3,4] Monika Szczepanowski,[5] Michael Baudis,[6] Susanne Bens,[1] Laurence de Leval,[7] Africa Garcia-Orad,[2] Heike Horn,[8] Jasmin Lisfeld,[3] Shoji Pellissery,[1] Wolfram Klapper,[5] Ilske Oschlies,[5] and Reiner Siebert[1]

[1]Institute of Human Genetics, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Kiel, Germany; [2]Department of Genetics, Physical Anthropology and Animal Physiology, University of the Basque Country, UPV-EHU, Spain; [3]NHL-BFM Study Center, Department of Pediatric Hematology and Oncology, Justus-Liebig-University, Giessen, Germany; [4]Pediatric Hematology and Oncology, University Hospital Münster, Germany; [5]Department of Pathology, Hematopathology Section and Lymph Node Registry, Christian-Albrechts University, Kiel, Germany; [6]Institute of Molecular Life Sciences, University of Zurich, Zurich, Switzerland and Swiss Institute of Bioinformatics, University of Zurich, Zurich, Switzerland; [7]Institute of Pathology, CHUV, University Hospital of Lausanne, Switzerland; and [8]Department of Clinical Pathology, Robert-Bosch-Hospital and Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology Stuttgart, Germany

Current address of Itziar Salaverria: "Institut d'Investigacions Biomèdiques August Pi i Sunyer", University of Barcelona, Hematopathology Section, Hospital Clínic, Barcelona, Spain

ABSTRACT

Pediatric follicular lymphoma is a rare disease that differs genetically and clinically from its adult counterpart. With the exception of pediatric follicular lymphoma with *IRF4*-translocation, the genetic events associated with these lymphomas have not yet been defined. We applied array-comparative genomic hybridization and molecular inversion probe assay analyses to formalin-fixed paraffin-embedded tissues from 18 patients aged 18 years and under with *IRF4* translocation negative follicular lymphoma. All evaluable cases lacked t(14;18). Only 6 of 16 evaluable cases displayed chromosomal imbalances with gains or amplifications of 6pter-p24.3 (including *IRF4*) and deletion and copy number neutral-loss of heterozygosity in 1p36 (including *TNFRSF14*) being most frequent. Sequencing of *TNFRSF14* located in the minimal region of loss in 1p36.32 showed nine mutations in 7 cases from our series. Two subsets of pediatric follicular lymphoma were delineated according to the presence of molecular alterations, one with genomic aberrations associated with higher grade and/or diffuse large B-cell lymphoma component and more widespread disease, and another one lacking genetic alterations associated with more limited disease.

Introduction

Follicular lymphoma (FL) is the most frequent indolent lymphoma in the Western world and accounts for approximately 20-40% of all B-cell lymphomas.[1] Pediatric FL is considered a variant of FL that differs from adult FL with an increased proportion exhibiting high-grade histology and most cases presenting clinically as localized and curable diseases.[2-4] Moreover, pediatric FL differs genetically from their adult counterpart.[2] The genetic hallmark of adult FL, the translocation t(14;18)(q32;q21) affecting the *BCL2* gene is hardly ever present in pediatric FL.[2,3] Overall, and in contrast to adult FL, the genetic events associated with pediatric FL pathogenesis and prognosis have not yet been defined, with the notable exception of those pediatric cases carrying an *IRF4* translocation.[4] Therefore, we applied array-comparative genomic hybridization (aCGH) and molecular inversion probe (MIP) assay adapted for formalin-fixed, paraffin-embedded (FFPE) tissues to FL of 18 patients diagnosed up to the age of 18 years.

Design and Methods

The study included 18 pediatric FL lacking an *IRF4* translocation with available FFPE tissue diagnosed in patients aged up to 18 years; the clinicopathological features of 10 of these cases have been reported previously.[3] With the exception of one case with only focal involvement by lymphoma (pFL13), the tumor cell content exceeded 50% in the evaluable samples. Eleven of 18 patients were treated according to NHL-BFM group multicenter trials,[5,6] whereas 7 were treated according to different treatment strategies. Clinical and histopathological data are summarized in the *Online Supplementary Appendix* and *Online Supplementary Table S1*.

DNA was extracted from FFPE tissue blocks using a phenol-chloroform extraction method.[7] Fourteen cases were hybridized on the MIP-assay using Oncoscan FFPE Express custom service (Affymetrix, Santa Clara, CA, USA).[8] Thirteen cases were analyzed using Agilent 244K array (Agilent Technologies, Santa Clara, CA, USA), including 9 cases simultaneously analyzed by MIP-assay (*Online Supplementary Appendix* and *Online Supplementary Figure S1*). Copy number (CN) plots were generated by the use of Nexus 6.0 beta Discovery Edition

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Correspondence: imartinguerrero@medgen.uni-kiel.de

software (Biodiscovery, El Segundo, CA, USA). Gains and losses were evaluated by 2 different observers.

Fluorescence *in situ* hybridization (FISH) analyses were performed for the detection of breakpoints or gene fusions and for verification of gains in chromosome 6p25 as previously described.[9,10] For this purpose, commercially available *MYC* BAP, *BCL2* BAP, *IGH* BAP and *BCL6* BAP probes, an *IGH/BCL2* double-color double-fusion probe (all Abbott/Vysis, Downers Grove, IL, USA) and a previously designed FISH probe for *IRF4* (BAP)[4] were used.

Potential point mutations detected by MIP-assay in *PIK3CA*, *FBXW7*, *ABL1*, *NOTCH1*, *STK11* and *PTEN* were also analyzed by direct sequencing using ABI PRISM 3100 Genetic Analyzer system (Applied Biosystems, Foster City, CA, USA). Details are described in the *Online Supplementary Appendix.* Similarly, the coding exons of TNFRSF14 (*Online Supplementary Table S2*) and Tyr641 *EZH2*[4] were also analyzed by direct sequencing in the whole series.

Clonality analysis was performed investigating the framework 1-3 regions of the immunoglobulin heavy chain (*IGH*) according to the Biomed-2 protocol.[11]

Statistical analyses were performed using PASW Statistics software version 18 (SPSS Inc., Chicago, IL, USA).

The study was performed in the framework of the BFM-NHL trial, for which central and local institutional review board (IRB) approvals were obtained, and according to the guidelines of the MMML Network Project of the Deutsche Krebshilfe (approved by the Institutional Review Board of the Medical Faculty Kiel under 403/05).

Results and Discussion

Pediatric FL is a rare disease that differs from its adult counterpart both genetically and clinically.[3] We recently described a distinct subset of germinal center B-cell lymphomas including FL characterized by the presence of *IRF4* gene translocations, predominately affecting children and young adults.[4] In the present study, we determined genetic aberrations in a series of 18 pediatric FL cases lack-

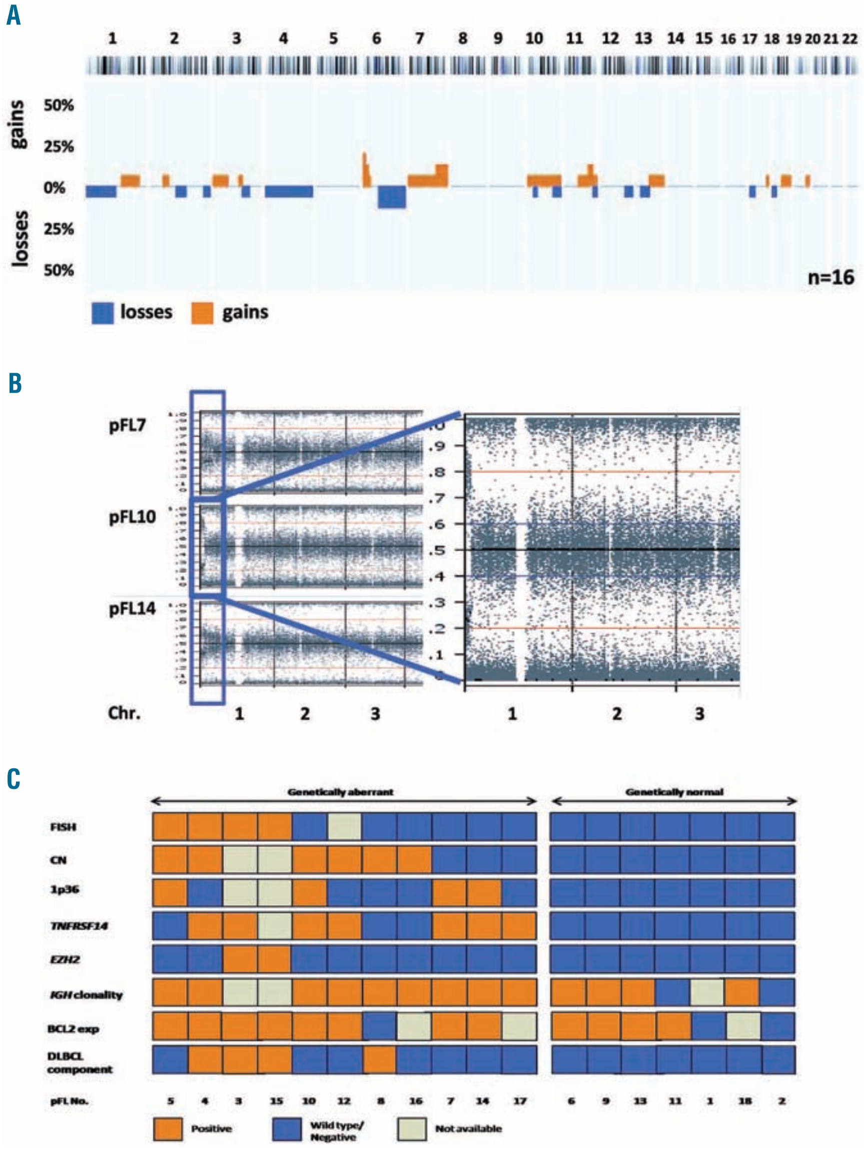

Figure 1. (A) Copy number (CN) profiles of 16 pediatric FL. In the x-axis the chromosomes are represented horizontally from 1 to 22, in the y-axis the percentage of cases showing the CN alterations. Gains are represented in the positive y-axis and colored in yellow, whereas losses are represented in the negative y-axis in blue. The most frequent CN alteration was gain/amplification of 6pter-p24.3. (B) Molecular Inverse Probe (MIP)-assay profiles showing CN neutral loss of heterozygosity (CNN-LOH) at 1p36 in the pFL7, pFL10 and pFL14 cases. Allelic events are displayed along the x axis (from pter to qter). Germ-line homozygosity (e.g. AA, BB alleles) at a given SNP results in calls at the 0 and 1 levels, respectively, germ-line heterozygosity (AB-alleles) in calls around 0.5 (y-Axis: 0-1). CNN-LOH in the tumor leads to loss of calls around 0.5 and to the presence of allelic imbalance calls derived from a sum of heterozygous normal cell (AB) and homozygous tumor cell (AA or BB) calls for a given locus resulting in values between 0-0.5 or 0.5-1 depending on the amount of cells carrying the aberration. Thus, in the areas when only contribution from one parent (LOH/CNN-LOH), two bands should we expected (0% and 100%->0 and 1.0. y Axis). In the 3 cases (pFL7, pFL10, pFL14), the probes did not reach such thresholds because alterations are detected to be in mosaicism (not germ-line alterations). (C) Summary data of the FISH, CN, CNN-LOH, 1p36, TNFRSF14, EZH2 mutation, IGH clonality, BCL2 expression analyses and DLBCL component for the 18 pediatric FL patients. FISH was considered positive when splits in the BCL2, BCL6, MYC, IRF4 and IGH genes were detected; CN, when chromosomal imbalances were found by MIP-assay or aCGH; 1p36, when CNN-LOH (detected by MIP-assay) or deletions (by MIP-assay and/or aCGH) were observed at that region; TNFRSF14 and EZH2, when mutations were found by direct sequencing; IGH clonality was positive when clonal IGH chain gene rearrangement was detected by PCR; BCL2 expression was positive when more than 25% of the cells were positive. In pFL2 only the region FR3 was evaluable in the IGH PCR reaction. In pFL18 IGH monoclonality was based on an analysis performed in an outside laboratory. CNN-LOH could not be determined in cases 1, 2, 12, 16, 17, and 18.

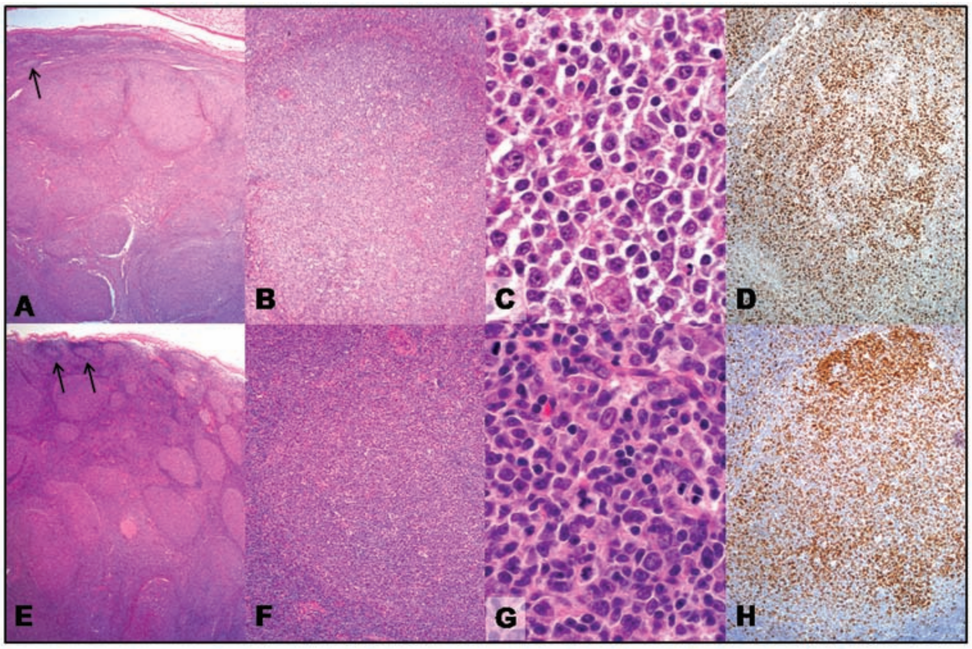

Figure 2. (A-H) Histomorphological features of case pFL11 (FL3a) (A-D) without aberrant genotype and case pFL14 (FL3a) (E-H) with aberrant genotype: in both cases an infiltration of the lymphnode by enlarged abnormal follicles as well as remnants of normal reactive follicles (indicated by arrows) are seen in the low magnification (A,E, H&E x 25). The neoplastic follicles lack a clear starry sky pattern as well as the demarcation by a mantle zone (B,F, H&E x 100). The follicles consist of centroblasts and centrocytes (C,G, H&E x 1000). The lack of zonation is seen with immunohistochemistry for the proliferation marker Ki67 (D, H, Ki67 x 100), nevertheless a hot spot of proliferation can be observed in H.

ing such *IRF4* translocation. Of these 18 FL, 9 (50%) were classified as FL grade 3a (FL3a), 6 (33%) as grade 3b (FL3b), one (6%) as grade 3 unclassified, and 2 (11%) as grade 2. Areas of grade 1 or 2 FL as a second lymphoma component were detectable in 4 cases diagnosed as FL3a (22%), while a simultaneous diffuse large B-cell lymphoma (DLBCL) component was noted in 4 (22%) cases, 3 diagnosed as FL3b and one as FL3a. Seven patients presented with stage I disease, 5 were rated as stage II and 3 suffered from stage III disease. Tumor localization in or dissemination to the neck region was the most frequent presentation (11 of 18). Notably, the present series of pediatric FL seems to differ from those of other recently published series with regard to sites of involvement, clinical stage and presence of a DLBCL component.[12,13] This might be due to the fact that the present series predominately reflects population-based assessment for a pediatric clinical trial rather than data collected from consultation centers. The patients were predominantly male (61%), with a median age of 12.1 years (range 6-18 years). All cases evaluable for the respective analyses lacked *BCL2* breakpoints and/or *IGH-BCL2* fusion and *MYC* breakpoints by FISH. Breaks in IGH locus occurred in 4 of 15 evaluable cases whereas a *BCL6* break occurred in one of 17 cases (*Online Supplementary Table S1*).

CN determination by aCGH and/or MIP-assay was successful in 16 of the 18 FL (89%) (*Online Supplementary Figure S1*). Eight samples were analyzed on both CN platforms showing a good agreement (with 7 showing the same imbalances by both platforms). Only one case (pFL12) with low quality DNA showed differences between platforms, with a chromosome 7 gain only detectable using MIP-assay. Only 6 of 16 evaluable pediatric FL (37%) displayed CN alterations and/or copy number neutral-loss of heterozygosity (CNN-LOH), with a mean of 6.5 aberrations per case (Figure 1A and *Online Supplementary Tables S3 and S4*). These findings contrast with adult FL, where the number of cases with chromosomal imbalances[14] and CNN-LOH[15] is higher (71.6% *vs.* 37.5%; *P*=0.01 and 76% *vs.* 40%; *P*=0.05, respectively). The most frequent imbalance in pediatric FL was 6pter-p24.3 gain including amplification (3 of 6 aberrant cases). Despite *IRF4* was shown by FISH to be included in the gained region (*Online Supplementary Figure S2*), no consistent expression of IRF4/MUM1 was observed in these cases (2 of 3 expressed IRF4/MUM1). Remarkably, 3 cases showed CNN-LOH in 1p36.32-p36.13 region (pFL7, pFL8, and pFL14) (Figure 1B) and another one showed a deletion of the whole 1p arm (pFL5). In comparison with 3 previously published pediatric FL cases positive for *IRF4* translocation,[16] cases positive for the translocation were significantly more complex in terms of CN alterations than the *IRF4* negative pediatric FL (7 alterations/case *vs.* 2.4 alterations/case; *P*=0.029) (*Online Supplementary Figure S3*). Of note, *IRF4* translocation positive cases presented more frequently gains of 11q and deletions of 17p arm including the *TP53* gene. Furthermore, one of the cases showed a deletion at 1pter-p35.2 with a transition mutation in the *TNFRSF14* gene (g.343C>T, T15I) (*data not shown*).

Both the gain in 6p as well as CNN-LOH/loss of 1p seem not to be exclusive to pediatric FL, since they have also been described in adult FL independently of the presence of t(14;18) translocation.[14] In fact, deletions and CNN-LOH of 1p36 have been described as one of the most frequent secondary genetic aberrations in adult FL[15] and are considered a significant predictor of poor overall survival.[17] The minimal region of loss/CNN-LOH in 1p36 contains the candidate gene *TNFRSF14*, encoding a member of the tumor necrosis factor receptor (TNFR) superfamily which has been shown to be recurrently mutated in adult FL.[18,19] Sequencing of *TNFRSF14* in the 4 pediatric FL cases with 1p36 aberration revealed 3 to carry mutations, including one missense mutation in exon 1 (g.340C>G, S14C; pFL7), two splice donor site mutations of the exon 1 (g.370T>C and g.370T>A; pFL7 and pFL10) and one nonsense mutation in exon 5 (g.4336C>T, Q180X; pFL14). Extension of the *TNFRSF14* mutation screening to the remaining cases revealed 5 non-synonymous mutations in 4 pediatric FL without 1p36 aberration (*Online Supplementary Table S5*). Thus, 7 of 17 pediatric FL contain mutations in *TNFRSF14* making this the most recurrent change in this disease known so far. In order to identify the incidence of previously described EZH2 protein mutation (Tyr641),[20] the whole series of pediatric FL was sequenced; 2 cases were found with mutated (pFL3 and pFL15) (*Online Supplementary Table S3*).

A synopsis of the obtained molecular profiling results revealed that all cases with breaks in *IGH* or *BCL6* also showed CN alterations and/or mutations in *TNFRSF14* or *EZH2* genes. Based on the results of the molecular analyses, two groups of FL could be distinguished: one containing the genetically aberrant pediatric FL and another one comprising the pediatric FL without any aberration (Figure 1C). The absence of genomic aberrations due to a low content of tumor cells was ruled out in all the patients (>50% tumor cell content) except in case pFL13 (20%). Nevertheless, we cannot rule out the possibility that the percentage of sub-clonal cells harboring a genetic aberration might influence the grouping.

Studying *IGH* clonality revealed that the 2 samples with polyclonal pattern (pFL2 and pFL11) were in the set lacking genomic aberrations. In one of the cases (pFL2), only the FR3 region was evaluable in the central *IGH* clonality analysis. Therefore, we cannot exclude that clonality could be detectable with FR1 or FR2 primers. Despite the polyclonal pattern, both cases displayed clear histomorphological features of malignancy with subtotal effacement of the underlying lymphnode structure, destruction of the normal germinal center architecture, loss of follicle mantles and abnormaly enlarged in part confluent neoplastic follicles. Although there is general agreement regarding the absence of *BCL2*-rearrangement in pediatric FL at the molecular level, reported levels of BCL2 protein expression vary considerably ranging from 0% to 50%.[2,3,12,13] In our series, the majority of the cases (12 of 15) expressed the protein to some degree. The relatively high proportion of BCL2 expressing cases in our series, in comparison to previous reports, might be due to the selection criteria applied, i.e. the inclusion cases of FL with simultaneous DLBCL component and excluding cases with *IRF4* translocations. No correlation was found between BCL2 expression and the presence of genetic aberrations.

Comparing the two groups defined by the genomic aberration status with clinical data, the group with aberrations was enriched for patients showing higher grade histology and higher stage disease patterns. For example, advanced disease stage (>II), grade 3b or a DLBCL component occurred almost exclusively in the genetically altered group (Table 1). In contrast, lack of genetic aberrations occurred in clinical stages I and II and was never associated with a DLBCL component, although this was not statistically significant probably because of the low number of cases (Figure 1C). Notably, comparing cases with and without neck region tumor localization/involvement, the second group was significantly associated with the presence of genomic aberrations (*P*=0.03). Previous studies have shown that tonsillar pediatric FL are nearly always positive for MUM1/IRF4.[13] Nevertheless, the present series shows few cases (pFL4 and pFL 15) with tonsillar involvement, which at least in part is likely due to exclusion of the cases harboring *IRF4* translocations known to be strongly MUM1 positive.[4]

Table 1. Comparison of clinical and biological characteristics of pediatric follicular lymphoma (FL) with genomic aberrations *versus* pediatric FL without aberrations.

Clinical and biological characteristics	Ped FL with genomic aberrations	Ped FL without genomic aberrations	*P*
Gender ratio (M:F)	1.2:1	2.5:1	0.64
Age (median)	12.1	12	0.97
Grade FL			0.31
1-2	1	1	
3a	4[a]	5[b]	
3b	5	1	
Grade 3 unknown	1	-	
Stage			0.11
I	2	5	
II	3	2	
III	3	0	
nd	3	-	
DLBCL component			0.12
No	7	7	
Yes	4[c]	0	
Localization			**0.03**
Neck region	4	7	
Other regions	4	0	
Both	3	0	
Remnants of reactive B follicles			0.38
No	5	2	
Yes	5	5	
nd	1	-	
Marginal zone differentiation			0.33
No	9	4	
Yes	2	3	
Ki67 (%)	55[d]	54[e]	0.99
Tumor cell content (%)	76.4	67.9	0.32
Median follow up (months)	73.8[e]	43.6	0.21

nd: not determined; DLBCL: diffuse large B-cell lymphoma; M: male; F: female. [a]One case with FL1/2 as a second lymphoma component; [b]Three cases with FL1/2 as a second lymphoma component; [c]Case pFL8 present "starry sky"/Burkitt-like pattern; [d]Data not available in one case; [e]Data not available in two cases.

Despite these biological differences, the overall survival was comparable between the groups with genomic aberrations and without them (Table 1 and *Online Supplementary Table S1*). This might be associated with the fact that most patients (12 of 16), besides the diagnostic lymph node excision, received treatment with multi-agent chemotherapy. The whole series showed an excellent survival with all patients being alive at the last follow up independently of the biological subgrouping, with a median follow up of 60.6 months.

In summary, we describe the pattern of genomic imbalances in *IRF4* translocation negative pediatric FL and identify recurrent mutation of *TNFRSF14*. Moreover, we show genetic alterations to distinguish two subsets of pediatric FL. In the first subset genomic aberrations could be identified with the techniques applied and this subset is associated with higher grade and/or diffuse large B-cell lymphoma component and more widespread disease. The second group lacks genetic alterations detectable with the present approaches and is associated with a more limited disease. Despite the absence of genomic aberrations, these cases resembled FL by their histopathological features (Figure 2). The absence of genetic aberrations detectable with the methods used in the current study does not necessarily mean that these lesions are completely devoid of genomic aberrations. Since the histopathology of these lesions is not compatible with reactive conditions, it seems possible that a higher resolution of genomic analysis such as next generation sequencing will reveal aberrations. In turn, the presence of genetic aberrations does not ultimately proof malignancy as documented, for example, in monoclonal gammopathy of undetermined significance (MGUS).[1] Indeed, it could well be that at least a subset of pediatric FL could similarly represent monoclonal follicular proliferations of undetermined significance.

Given that the patients included in this study have been treated independently of the genomic aberration status and show excellent survival rates, we cannot, therefore, comment on whether the detectability or pattern of genomic differences also translate into a different clinical outcome or whether the genetically normal appearing FL might be treated less intensively or if a "watch and wait" approach can be adopted in completely resected local disease.

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Authorship and Disclosures

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