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T(14;18)(q32;q21) involving *MALT1* and *IGH* genes occurs in extranodal diffuse large B-cell lymphomas of the breast and testis

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Primary B-cell lymphoma of the testis, breast and thyroid are rare and data concerning cytogenetic aberrations at these extranodal sites are scarce. We examined the presence of extranodal marginal zone lymphoma-associated translocations, t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21), t(3;14)(p14.1;q32) and numerical aberrations of chromosomes 1, 3, 12 and 18 by fluorescence *in situ* hybridization in 6 extranodal marginal zone lymphomas and 24 diffuse large B-cell lymphomas with (*n* = 9) or without (*n* = 15) marginal zone lymphoma components, with primary localizations in the breast (*n* = 15), testis (*n* = 9) and thyroid (*n* = 6). We found t(14;18)(q32;q21), with breakpoints in *IGH* and *MALT1*, in one testicular diffuse large B-cell lymphoma and in two diffuse large B-cell lymphomas of the breast. No other translocations, amplifications or deletions involving *IGH, BCL-10, BCL-2, MALT1* and *IAP2* were detected. Numerical aberrations occurred in 67% of the lymphomas, 67% of extranodal marginal zone lymphomas, 56% of diffuse large B-cell lymphomas with marginal zone lymphoma components and in 73% of '*de novo*' diffuse large B-cell lymphomas. These included 78% of testis, 67% of thyroid and 60% of breast lymphomas, and included mainly trisomy 18 (*n* = 16), trisomy 3 (*n* = 8) and trisomy 1 (*n* = 3). One testicular diffuse large B-cell lymphoma harbored both t(14;18)(q32;q21) and trisomy 3. Our results indicate that at least a few cases of diffuse large B-cell lymphoma of the testis and the breast belong to the spectrum of extranodal marginal zone lymphoma.
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Primary B-cell lymphoma of the testis, breast and thyroid are rare, each accounting for between 0.5 and 2.5% of all non-Hodgkin's lymphomas (NHLs).[1–6] Diffuse large B-cell lymphoma is the most common histological entity at these extranodal sites. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, commonly found in extranodal sites devoid of native lymphoid tissue, like the stomach, lung, salivary gland, thyroid and ocular adnexa, occur infrequently in the breast and testis. Although extranodal marginal zone lymphoma and diffuse large B-cell lymphoma are considered distinct clinicopathological entities in the World Health Organization (WHO) classification,[7] many extranodal diffuse large B-cell lymphomas have derived from a background of extranodal marginal zone lymphoma.[8–11] We found that a large subgroup of primary testicular diffuse large B-cell lymphoma has marginal zone lymphoma components, including small cell components and lymphoepithelial lesions.[12]

Four mutually exclusive and apparently site-specific, chromosomal translocations have been implicated in the development and progression of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. These extranodal marginal zone lymphoma-associated translocations, t(11;18)(q21;q21),[11,13–22] t(1;14)(p22;q32),[13,14,23] t(14;18)(q32;q21)[14,15,24,25] and t(3;14)(p14.1;q32)[26] show substantial differences in prevalence at specific extranodal localizations. In addition, several studies have reported the presence of various cytogenetic numerical aberrations, including trisomy 3, 7, 12 and 18, in extranodal marginal zone lymphoma

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at different extranodal sites.[8,15,17,27–35] One may wonder whether these extranodal marginal zone lymphoma-associated translocations and numerical aberrations occur in extranodal diffuse large B-cell lymphoma with marginal zone lymphoma components, which may belong to the extranodal marginal zone lymphoma spectrum.

This study investigated for the presence of extranodal marginal zone lymphoma-associated translocations and numerical aberrations in diffuse large B-cell lymphoma with and without extranodal marginal zone lymphoma components and in extranodal marginal zone lymphoma of the breast, testis and thyroid, to test the hypothesis that also these lymphomas may belong to the spectrum of extranodal marginal zone lymphoma.

Materials and methods

Patients and Tissue Samples

Formalin-fixed paraffin-embedded tissue samples of biopsies or surgical resection specimens of 30 B-cell lymphoma cases of the thyroid ($n = 6$), testis ($n = 9$) and breast ($n = 15$) were retrieved from the registries of the Comprehensive Cancer Centers South and West in the Netherlands. All cases were part of B-cell NHL series of three earlier publications,[12,36,37] and these patients were diagnosed between January 1981 and January 1999.

Biopsies from 30 patients, including 6 extranodal marginal zone lymphoma and 24 diffuse large B-cell lymphoma cases, were available for this study. Nine diffuse large B-cell lymphomas harbored marginal zone lymphoma features, which we defined as a small cell component with or without lymphoepithelial lesions, and were classified as diffuse large B-cell lymphoma with marginal zone lymphoma component.

For the diagnosis of the thyroid, testicular or breast lymphoma an adequate tissue biopsy of this site was required. Haematoxylin and eosin sections were examined, and all cases were reclassified according the WHO classification.[7] Prior immunophenotyping results were reviewed and, if necessary, additional staining was performed, including paraffin and frozen section immunohistochemistry. A variety of antibodies were used, including anti-CD3, CD5, CD10, CD20, CD45, CD79a, terminal deoxynucleotidyl transferase, cyclin D1 and anti-immunoglobulin heavy and light chains.

Fluorescence *In Situ* hybridization (FISH) Analysis

Sample preparation. Nuclei were isolated from the paraffin-embedded tissues as described previously.[17] Briefly, 50-μm thick sections were dewaxed by xylene, disaggregated manually and digested with 0.1% protease in phosphate-buffered saline for 40 min at 37°C. To make the target DNA accessible to the probes, the nuclear suspension was spun onto slides and subsequently incubated in a solution of 1 mol/l NaSCN at 80°C for 30 min and in 0.1% pepsin (Sigma-Aldrich), pH 2.0 at 37°C for 5–30 min.

Probe selection. Differentially labeled sets of probes were selected for detection of breaks, amplifications or deletions in the selected chromosomal regions. For detection of t(11;18)(q21;q21), two YAC clones were pooled to enhance the signal, both spanning the *IAP2* gene at 11q21 (YAC949B6 and YAC817C6) and the *MALT1* gene at 18q21 (YAC906C5 and YAC892F3).[29] For t(14;18)(q32;q21) detection, cosmid cosIg6 containing the *IGH C3* gene and surrounding sequences of region 14q32, and YAC906C5 and YAC892F3 (for the *MALT1* gene at 18q21) were used. For detection of t(1;14)(p22;q32) YAC 928EL spanning the *BCL-10* gene at 1p22 and cosmid cosIg6 at 14q32 were chosen. For t(14;18)(q32;q21) involving *IGH* and *BCL-2*, we used LSI IGH and LSI BCL2 probes obtained from Vysis (Downers Gove, IL, USA). All YAC clones were obtained from Centre d'Étude du Polymorphisme Humain Paris, France. DOP-PCR products of cosmids and YAC clones were labeled either with biotin-11-dUTP or with digoxigenin-11-dUTP (Roche, Mannheim, Germany). For the detection of trisomies (peri-)centromeric repetitive α-satellite DNA probes specific for chromosomes 1, 3 (D3Z1, Oncor Gaithersburg, MD, USA), 12 (pα12H8) and 18 (L1.84) were selected.[34] All probes were hybridized on metaphase spreads of lymphocytes to confirm chromosomal location and specificity.

FISH conditions and detection. FISH was performed as described previously.[29] In short, the labeled DNA probes were diluted in hybridization mixture (50% formamide, 2× standard saline citrate pH 7.0, 10% dextran sulfate (Pharmacia, Uppsala, Sweden), 0.2 μg/μl herring sperm DNA (Roche) and 10 μg/μl Cot1 DNA (Roche) to a final concentration of 20 μg/μl. A volume of 10 μl of hybridization mixture was added onto the slide; probe and target DNA were denatured for 8 min at 80°C. After overnight hybridization at 37°C, the slides were washed in 50% formamide/2× SSC (2 × 10 min at 45°C) and 2 × 5 min in 0.1× SSC/0.05% Tween-20 at 60°C. Probes were detected by fluorescein isothiocynate and Texas red isothiocynate-labeled antibodies as described previously.[29] FISH conditions, washes and detection for LSI IGH/BCL2 probes were performed according to the manufacturer's protocol (Vysis).

Normal controls. To determine the cutoff level in normal interphase nuclei, FISH was performed on cytospin preparations from eight reactive tonsils. At least 4 × 200 qualifying nuclei per slide were evaluated on a DMRB/E fluorescence microscope (Leica, Wetzlar, Germany). The cutoff levels were

defined by the mean + 3s.d. Only cases with a complete pattern of one separate red signal, two separate green signals and one co-localized or fused signal (1R2G1F) were considered consistent with t(1;14)(p22;q32) or t(14;18)(q32;q21), using the appropriate probe sets. Nuclei with an incomplete set of signals were omitted from the score. Signals were considered co-localized when their distance was equal to or smaller than the size of the hybridization signal. A pattern of 1R1G2F was indicative for the presence of t(11;18)(q21;q21). Criteria for trisomy detection were described previously.[34] The cutoff levels determined for individual probe sets ranged from 2.1 to 2.7% for YAC and cosmid probes and between 5 and 7% for the various centromeric probes.

Results

We found t(14;18)(q32;q21), with breakpoints in *IGH* and *MALT1*, in three diffuse large B-cell lymphomas, including one testicular diffuse large B-cell lymphoma and two diffuse large B-cell lymphomas of the breast, one of which was a diffuse large B-cell lymphoma with marginal zone lymphoma component (Table 1). The t(14;18)(q32;q21)-positive lymphomas showed split signals for the *MALT1* probe, confirming *MALT1* involvement in the translocation, and co-localization to one *IGH* C region probe signal (Figure 1). Rearrangement of the *IGH* locus was confirmed by FISH with LSI *IGH* probes showing split signals, while the absence of *IGH/BCL2* fusions pointed to a lack of *BCL-2* involvement in the translocation. The number of nuclei with a translocation in t(14;18)(q32;q21)-bearing lymphomas ranged from 15 to 20%, well above the cutoff level of 2.1%. Other breaks, involving *IGH*, *BCL-10*, *MALT1*, *BCL-2* and *IAP2*, amplification or deletion of chromosomal region 11q21, 18q21, 1p22 and 14q32, were not detected.

Numerical chromosomal aberrations occurred in 67% (4/6) of the extranodal marginal zone lymphomas, 73% (11/15) of the diffuse large B-cell lymphomas and 56% (5/9) of the diffuse large B-cell lymphomas with extranodal marginal zone lymphoma component (Table 2). Trisomy 18 was most commonly found ($n = 16$), followed in decreasing order of frequency by trisomy 3 ($n = 8$), trisomy 1 ($n = 3$), trisomy 12 ($n = 1$) and tetraploidy of chromosomes 18 ($n = 2$) and 3 ($n = 1$). Trisomies 3 and 18 were encountered in all three histological subtypes; trisomy 1 was exclusively found in diffuse large B-cell lymphomas with or without extranodal marginal zone lymphoma component, and trisomy 12 was found in one case of diffuse large B-cell lymphoma. Multiple chromosomal aberrations were more commonly found in testicular diffuse large B-cell lymphomas with and without extranodal marginal zone lymphoma component than in diffuse large B-cell lymphomas at other sites. One case, displaying three IAP2 probe signals, was confirmed with trisomy 11 using chromosome 11 specific centromeric probe ($n = 1$). One t(14;18)(q32;q21)-positive testicular lymphoma in addition harbored trisomy 3.

Discussion

This is the first report showing the presence of an extranodal marginal zone lymphoma-associated translocation in diffuse large B-cell lymphomas of the breast and testis. Two of the three t(14;18)(q32;q21)-positive diffuse large B-cell lymphomas lacked extranodal marginal zone lymphoma components and this translocation might therefore not be specific for extranodal marginal zone lymphoma-associated lymphomas. Alternatively, lack of marginal zone lymphoma components is not proof of a '*de novo*' diffuse large B-cell lymphoma, as the possibility of a marginal zone lymphoma component that is no longer apparent is more likely. We did not find any of the extranodal marginal zone lymphoma-associated translocations in extranodal marginal zone lymphoma of the breast and thyroid. Several studies have looked for extranodal marginal zone lymphoma-associated translocations in breast lymphomas.[13–15,27,38–40] T(18q21), involving *MALT1*, has not been found in any of the 36 extranodal marginal zone lymphomas and 14 diffuse large B-cell lymphomas[13–15,27,38–40] of the breast that have been reported to date. There are no reports of extranodal marginal zone lymphoma-associated translocations in testicular diffuse large B-cell lymphoma, as the presence of extranodal marginal zone lymphoma components in testicular diffuse large B-cell lymphoma has been described only recently.[12] We did not find any structural aberrations in the thyroid lymphomas in our series. Other studies have confirmed the absence of t(14;18)(q32;q21) in thyroid lymphomas,[13,16,27,41] however, t(11;18) and t(3;14) have been reported in extranodal marginal zone lymphoma of the thyroid.[14,26,32,38] Several studies have confirmed differences in prevalence of extranodal marginal zone lymphoma-associated translocations at various anatomic sites and suggest that distinct molecular pathways are involved in the pathogenesis of extranodal marginal zone lymphoma.[42–44]

Interestingly, we found t(14;18)(q32;q21), a translocation previously reported to be associated with extranodal marginal zone lymphoma, in lymphomas, which were diagnosed as diffuse large B-cell lymphoma. One case had evidence of a concomitant extranodal marginal zone lymphoma component, but this component lacked in the other two t(14;18)(q32;q21)-positive cases. These two diffuse large B-cell lymphomas may have been derived from transformed t(14;18)(q32;q21)-positive extranodal marginal zone lymphomas in which all small lymphoid cells were overgrown by blasts after

Table 1 Clinicopathological and FISH data of extranodal marginal zone lymphoma and diffuse large B-cell lymphoma of the thyroid, testis and breast for detection of t(11;18)(q21;q21) (t(1;14)(p22;q32), t(14;18)(q32;q21) involving *IGH/MALT1* and *IGH/BCL-2* and numerical aberrations of chromosomes 1, 3, 12 and 18

Patients	*Sex/ age*	*Origin*	*Histology*	*AAS*	*IPI*	*Site of relapse*	*Follow-up (months)*	*Structural and Numerical aberration*
1	f/48	Thyroid	EMZL	IV	3	Bone marrow, para-aortic and mesenteric LN	132 (Alive)	Trisomy 18
2	F/52	Thyroid	EMZL	IE	3	None	135 (AR)	Trisomy 3
3	M/54	Thyroid	EMZL	IE	0	None	240 (AR)	—
4	F/67	Thyroid	DLBCL	IV	Unknown	Hilar LN	7 (DP)	Trisomy 3, 18
5	F/65	Thyroid	DLBCL	IIE	1	None	130 (DI)	—
6	F/81	Thyroid	DLBCL	IE	3	None	1 (DI)	Trisomy 18
7	M/82	Testis	DLBCL + EMZL	IE	1	Pleura	30.6 (DP)	—
8	M/78	Testis	DLBCL + EMZL	IE	1	None	82.8 (DI)	Tetraploidy18
9	M/69	Testis	DLBCL + EMZL	IIE	2	None	50.8 (DU)	Trisomy 1, 3, 18
10	M/72	Testis	DLBCL + EMZL	IV	3	Bone marrow and stomach	44.7 (DP)	Trisomy 1, 3, 18
11	M/83	Testis	DLBCL	IIE	1	CNS	10.8 (DI)	T(14;18) IGH/MALT1, Trisomy 3
12	M/76	Testis	DLBCL	IIIE	3	None	10.8 (DI)	Trisomy 3, 18
13	M/58	Testis	DLBCL	IIE	1	CNS and eyes	12 (DP)	—
14	M/88	Testis	DLBCL	IIE	2	Para-aortic, iliac and mediastinal LN	2.6 (DP)	Trisomy 12, 18
15	M/76	Testis	DLBCL	IIE	2		1.2 (DC)	Trisomy 18
16	F/62	Breast	EMZL	IE	1	None	134 (AR)	Trisomy 18
17	F/65	Breast	EMZL	IE	1	None	74 (AR)	—
18	F/74	Breast	EMZL	IIIE	2	Para-vertebral muscles and chest wall	66 (AR)	Trisomy 3, 18
19	F/62	Breast	DLBCL + EMZL	IE	1	None	218 (AR)	T(14;18) IGH/MALT1
20	F/60	Breast	DLBCL + EMZL	IIE	0	None	153 (AR)	Trisomy 18
21	F/65	Breast	DLBCL + EMZL	IIIE	4	Stomach; cervical LN	13 (DP)	—
22	F/53	Breast	DLBCL + EMZL	IE	0	CNS	41 (DI)	—
23	F/69	Breast	DLBCL + EMZL	IE	1	None	50 (AR)	Trisomy 18
24	F/81	Breast	DLBCL	IE	3	None	67 (DU)	Trisomy 18
25	F/65	Breast	DLBCL	IE	1	Supraclavicular, mediastinal, para-aortic and iliac LN	25 (AP)	Tetraploidy 3, 18
26	F/89	Breast	DLBCL	IV	3	None	4 (DU)	Trisomy 18
27	F/83	Breast	DLBCL	IE	Unknown	None	11 (DI)	Trisomy 11, 18
28	F/56	Breast	DLBCL	IIE	0	None	101 (AR)	T(14;18) IGH/MALT1
29	F/85	Breast	DLBCL	IE	1	Pleura; mediastinal, suprclavicular, para-aortic LN	11 (DP)	Trisomy 1, 3, 18
30	F/73	Breast	DLBCL	IE	Unknown	CNS	54 (DP)	—

Abbreviations: AL, alive; AP, alive, with progressive disease; AR, alive and in remission; CT, chemotherapy; DI, death due to an intercurrent cause; DP, death due to disease progression; DU, death due to unknown cause; F, female; FISH, fluorescence in situ hybridization; LN, lymph nodes; M, male; RT, radiation therapy; S, surgery.

secondary tumor transformation. This hypothesis conflicts with data of previous research from our group on cutaneous extranodal marginal zone lymphoma that showed lack of blastic transformation in the cases that harbored the t(14;18)(q32;q21).[29] Alternatively, t(14;18)(q32;q21) may also be present in '*de novo*' diffuse large B-cell lymphoma, as previously reported in one case of cutaneous diffuse large B-cell lymphoma,[45] and as was previously shown for another extranodal marginal zone lymphoma-associated translocation t(3;14)(p14.1;q32)) involving *IGH* or *IGL* and *FOXP1*.[46,47]

We found breakpoints in the *IGH* JH region and noncoding region *MALT1* or exon 1 *MALT1*, which is in agreement with previously reported data.[25] By using an extensive panel of probes for all genes that have been associated with translocations in extranodal marginal zone lymphoma, we could exclude the presence of other extranodal marginal zone lymphoma-associated translocations, such as t(1;14)(p22;q32), t(11;18)(q21;q21), and in addition t(14;18)(q32;q21) involving *IGH* and *BCL-2*, which is characteristic of follicular lymphoma. Moreover, we did not detect t(3;14)(p14.1;q32)) involving *IGH* or *IGL* and *FOXP1* found in extranodal marginal zone lymphoma and diffuse large B-cell lymphoma.[26,46,47]

We did not detect any new or recently described sporadic translocations, such as t(6;7)(q25;q11),[48] t(X;14)(p11.4;q32),[49] and translocations involving chromosomal regions on chromosome arms 1p, 1q, 5q and 9p.[48] No loss or amplification of any of the studied regions was seen.

Similarly to other studies we found that trisomies 3 and 18 were the most common numerical aberrations in extranodal marginal zone lymphoma,[14,17,24,27,31,32,35,50,51] and extranodal diffuse

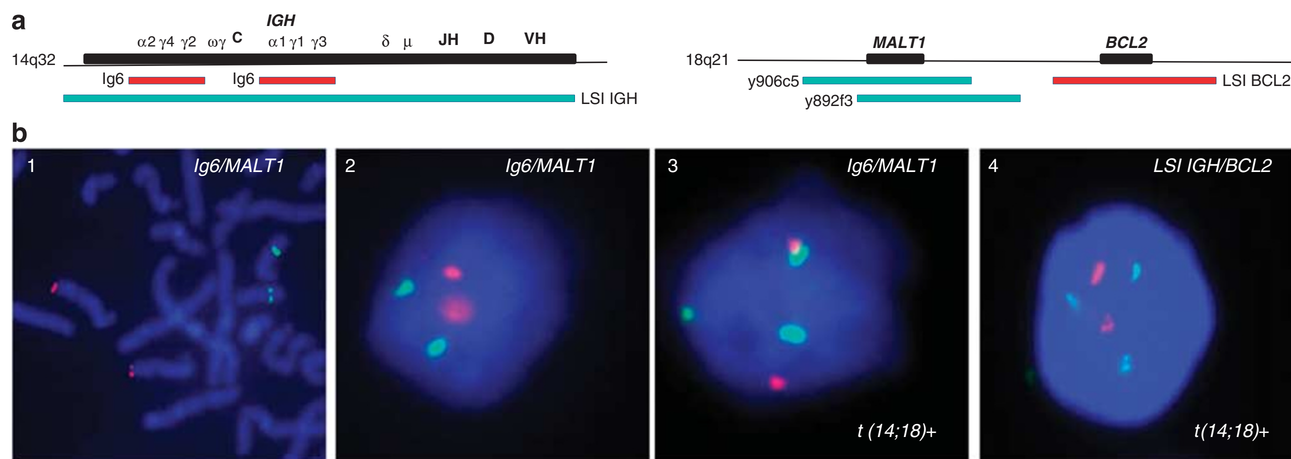

Figure 1 Fluorescence *in situ* hybridization (FISH) assay for detection of t(14;18)(q32;q21). (**a**) Illustrates the positions of the differentially labeled YAC and cosmid clones used as sets for detection of breaks t(14;18)(q32;q21) involving *IG6/MALT1* or LSI *IGH/* LSI BCL-2 Vysis (distances are not drawn to scale). (**b**) Probes were hybridized to normal metaphase lymphocyte nuclei (1) or interphase nuclei isolated from formalin-fixed paraffin-embedded tumor tissue (2, 3 and 4). 1 and 2 depict the signal pattern in translocation-negative nuclei. The translocation t(14;18)(q32;q21) results as a separate red (chromosome 14), two separate green signals (chromosome 18 and derivative chromosome 18) and one co-localized or fused red/green 1R2G1F (derivative chromosome 14) hybridized with *IGH/MALT1* probes (3). LSI *IGH* and *BCL-2* resulted in a 3G2R pattern in t(14;18)-positive lymphoma (4). Images were captured using quantix cooled CCD camera (Photometrics) attached to a DMRB/E fluorescence microscope (Leica) and IPlab Images acquire plus analysis software (IPlab) and were processed using Adobe Photoshop (version 5.5, Adobe Systems, CA, USA).

Table 2 Chromosomal aberrations and translocation in extranodal marginal zone lymphoma and diffuse large B-cell lymphoma of the thyroid gland ($n=6$), testis ($n=9$) and breast ($n=15$)

Chromosomal aberration	*EMZL* (n = 6; %)	*DLBCL* (n = 15; %)	*DLBCL + EMZ* (n = 9; %)	*DLBCL total* (n = 24; %)
T(14;18)	0	13	11	13
Trisomy 18	50	60	44	54
Trisomy 12	0	7	0	4
Trisomy 11	0	7	0	4
Trisomy 3	33	27	22	25
Trisomy 1	0	0	22	8
Tetraploidy	0	7	11	8
1 chromosomal aberration	17	47	22	38

large B-cell lymphoma.[33] We found a similar proportional distribution of the trisomies 18 and 3 in diffuse large B-cell lymphoma and extranodal marginal zone lymphoma at these extranodal sites. Patients with '*de novo*' diffuse large B-cell lymphoma harbored more frequently two or more numerical aberrations compared with patients with extranodal marginal zone lymphoma and diffuse large B-cell lymphoma with extranodal marginal zone lymphoma component. One of our three cases with t(14;18)(q32;q21) had an additional trisomy 3.

In conclusion, our results indicate that t(14;18)(q32;q21) involving *IGH-MALT1* is not restricted to extranodal marginal zone lymphoma but can occasionally be found in '*de novo*' extranodal diffuse large B-cell lymphoma of the breast and testis. The presence of this translocation in a diffuse large B-cell lymphoma of the breast with extranodal marginal zone lymphoma features could indicate that at least some cases of diffuse large B-cell lymphoma of the breast may belong to the spectrum of extranodal marginal zone lymphoma.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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