Modern Pathology (2006) 19, 1402–1408

www.modernpathology.org

MALT1 gene rearrangements and NF-κB activation involving p65 and p50 are absent or rare in primary MALT lymphomas of the breast

Sameer S Talwalkar*, Jose R Valbuena, Lynne V Abruzzo, Joan H Admirand, Sergej N Konoplev, Carlos E Bueso-Ramos and L Jeffrey Medeiros

Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Mucosa associated lymphoid tissue (MALT) lymphomas arising in the breast are uncommon and few cases have been assessed for MALT lymphoma-associated translocations, BCL-10 expression, or NF-κB activation. In this study, we analyzed eight cases of primary breast MALT lymphoma. We also included 14 cases of primary breast diffuse large B-cell lymphoma since some of these may represent transformation of MALT lymphoma, known to occur at extra-mammary MALT sites. All cases were assessed for *MALT1* gene rearrangements by fluorescence *in situ* hybridization (FISH). Using immunohistochemical methods, all cases were assessed for BCL-10, and subsets were assessed for NF-κB p65 and p50. None of the cases had *MALT1* gene rearrangements by FISH. Of eight MALT lymphomas, BCL-10 was positive in seven (88%), with moderate nuclear and cytoplasmic staining in six, and a weak cytoplasmic staining in one. NF-κB p65 ($n=8$) and p50 ($n=5$) were negative or showed only cytoplasmic staining (ie inactivated) in all cases. Of 14 diffuse large B-cell lymphoma cases, BCL-10 was positive in 12 (87%), with weak-to-moderate cytoplasmic staining in 10, weak cytoplasmic and focally nuclear staining in one, and a moderate-to-strong nuclear and cytoplasmic staining in one. NF-κB p65 ($n=11$) showed cytoplasmic staining in all cases, whereas p50 ($n=8$) showed nuclear positivity (ie activated) in two (25%) cases. We conclude that *MALT1* gene rearrangements are absent or rare in primary breast MALT lymphoma and diffuse large B-cell lymphoma. In MALT lymphomas, the moderate BCL-10 nuclear expression in six neoplasms is inconsistent with the FISH results, suggesting that BCL-10 immunostaining overestimates the frequency of *MALT1* gene rearrangements. We also could not demonstrate NF-κB activation using nuclear staining for p65 and p50. In contrast, breast diffuse large B-cell lymphomas are heterogeneous. Weak cytoplasmic BCL-10 staining in most cases and evidence of NF-κB p50 activation in a subset differs from breast MALT lymphomas.
Modern Pathology (2006) **19,** 1402–1408. doi:10.1038/modpathol.3800668; published online 18 August 2006

Keywords: breast; DLBCL; MALT-lymphoma; *MALT1* gene; NF-κB p65

Malignant lymphomas involving the breast are most commonly non-Hodgkin lymphomas that may either be localized, presumably arising in the breast (ie primary breast lymphoma) or a manifestation of systemic disease.[1,2] The most common histologic types of primary breast lymphoma are diffuse large B-cell lymphoma and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), so-called MALT lymphoma.[1,2]

The molecular pathogenesis of MALT lymphomas arising in the breast is not well established, presumably because they are uncommon. However, cytogenetic and molecular studies of MALT-lymphoma at extra-mammary extranodal sites have shown the presence of distinctive chromosomal translocations in a subset of cases. These translocations include the t(11;18)(q21;q21), t(14;18)(q32;q21), t(1;14)(q22;q32), and the most recently described, t(3;14)(p14.1;q32).[3–5] The t(11;18) creates a novel *API2-MALT1* fusion gene. The t(14;18), t(1;14), and t(3;14) juxtapose the *MALT1*, *BCL-10*, and *FOXP1* genes, respectively, with the immunoglobulin heavy chain (*IgH*) gene. These translocations appear to be mutually exclusive and show substantial differences in their frequency that correlate with anatomic

Correspondence: Dr LJ Medeiros, MD, Department of Hematopathology, Box 72, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
E-mail: ljmedeiros@mdanderson.org

*Dr Talwalkar did this work as a visiting resident supported by a College of American Pathology Foundation Training in technology Award. His current address is Department of Pathology, University of Louisville, Louisville, Kentucky, USA.
Received 20 December 2005; revised and accepted 5 July 2006; published online 18 August 2006

site.[3–5] The t(11;18) is most frequent in MALT lymphomas of the lung and stomach. In contrast, the t(14;18) is more common in MALT lymphomas arising in the ocular adnexae and liver, and the t(3;14) is common in MALT lymphomas of the thyroid gland, ocular adnexae, and skin. The t(1;14) is rare, but in separate studies was found most often in MALT lymphomas of the lung and intestine.[3,5] With the possible exception of the t(3;14), which is not well characterized to date, these translocations result in downstream activation of the NF-κB pathway.[6–8]

The molecular pathogenesis of primary diffuse large B-cell lymphomas of the breast is also not established. However, at extra-mammary extranodal sites, such as the stomach, diffuse large B-cell lymphomas arising from low-grade MALT lymphoma is well described.[9,10] Furthermore, patients with gastric diffuse large B-cell lymphomas (without MALT lymphoma) have been shown to have a high frequency of serum antibodies specific for *Helicobacter pylori,* suggesting that some cases of gastric diffuse large B-cell lymphomas arise from benign MALT tissue.[11] It seems reasonable, therefore, to hypothesize that the pathogenesis of some cases of primary breast diffuse large B-cell lymphomas may be related to MALT lymphoma.

In this study, we collected cases of primary breast MALT-lymphoma and diffuse large B-cell lymphomas to assess for *MALT1* gene rearrangements, pattern of BCL-10 immunostaining, and NF-κB activation using antibodies specific for p65 (Rel A) and p50. Our primary goal was to determine if chromosomal translocations and NF-κB activation, reported in MALT-lymphomas that involve a variety of extranodal sites, also occur in MALT lymphoma and a subset of diffuse large B-cell lymphomas localized to the breast.

Materials and methods

Clinical Information

The files of The University of Texas MD Anderson Cancer Center from January 1984 to the time of writing were searched for patients with primary breast lymphoma. The criteria to establish the diagnosis of primary breast lymphoma were based on those proposed by Wiseman and Liao.[12] These criteria include: (1) a biopsy specimen involved by lymphoma that shows a close relationship between the breast parenchyma and the neoplasm; and (2) affected patients have no evidence of systemic disease after staging. The criteria allow for ipsilateral axillary lymph node involvement in cases of primary breast lymphoma. However, in some biopsy specimens, particularly in needle biopsy specimens, we could not identify a close relationship between lymphoma and breast epithelium. In these cases, we also accepted a breast lymphoma as primary if radiologic studies clearly identified the neoplasm to be within the breast.

A total of 32 cases were identified. All cases were classified using the criteria of the World Health Organization classification; 29 of 32 (91%) were either MALT lymphoma ($n=10$) or diffuse large B-cell lymphomas ($n=19$). From this group, we selected eight MALT lymphomas and 14 cases of diffuse large B-cell lymphomas for additional studies based on the availability of either unstained tissue sections or paraffin blocks.

Histologic and Immunohistochemical Techniques

Biopsy specimens were routinely fixed and processed, and hematoxylin and eosin-stained slides were prepared. Immunohistochemical analysis was performed using fixed, paraffin-embedded tissue sections. Various antibody panels were used over the years, but all cases were assessed with antibodies specific for markers of B-cell and T-cell lineage. Some immunostains were performed at the referring institution at the time of initial diagnosis. More recently, immunostaining was performed in our laboratory using heat-induced epitope retrieval, an avidin–biotin complex method, and an automated immunostainer (Ventana Medical System, Tucson, AZ, USA) as previously described.[13] All 22 neoplasms in this study were shown to be of B-cell lineage.

As part of this study, additional immunostains were performed using antibodies specific for BCL-10 (monoclonal, 1:40) (Zymed, San Francisco, CA, USA), NF-κB p65 (polyclonal, 1:200) (Abcam, Austin, TX, USA) and p50 (polyclonal, 1:100) (Cell Signaling Technology, Beverly, MA, USA) as previously described.[14] The pattern of BCL-10 staining was categorized as cytoplasmic, cytoplasmic and nuclear, or negative, and the staining intensity was judged visually to be weak, moderate, or strong. NF-κB p65 and p50 immunoreactivity were categorized as either cytoplasmic (not activated) or nuclear with or without cytoplasmic staining (activated). The positive and negative controls for BCL-10 and NF-κB have been described previously.[14]

FISH Analysis

Fluorescence *in situ* hybridization (FISH) for *MALT1* gene rearrangement was performed using the LSI MALT1 (18q21) dual color, break-apart probe (Vysis, Downers Grove, IL, USA) according to the manufacturer's recommendations. Tissue sections 4 μm thick were placed onto slides, air dried, and baked overnight at 60°C. Slides were deparaffinized in CitriSolv (Fisher, Vernon Hills, IL, USA) three times for 5 min (min), and then immersed in 100% ethanol twice for 1 min. After air-drying, slides were treated in the Paraffin Pretreatment solution (Paraffin Pretreatment Kit II, Vysis) for 10 min, washed with purified water for 3 min at room temperature, and treated in the protease solution for 15 min at 37°C. Slides were then rinsed in purified water for 3 min,

air dried, and put in 2× SSC at 37°C for 30 min, dehydrated in 70, 85, and 100% ethanol, respectively, and allowed to air-dry. Hybridization mixture (10–20 ml) (Vysis) was applied to the slides, and denaturation was performed at 73°C for 3 min. The hybridization was performed at 37°C overnight in a moist chamber. Excess probe was washed away using 2× SCC/0.3% NP-40 (Fisher) at 73°C three times for 3 min, and the nuclei were counterstained with DAPI/Vectashield.

For scoring, the tissue sections were examined under a Zeiss fluorescence microscope using a ×100 oil immersion lens. Two technologists each scored 100 interphase nuclei at different sites for a total of 200 nuclei. Only cells with a one yellow (fusion), one green, and one orange signal were considered positive for *MALT1* gene rearrangement. Signals were considered co-localized when their distance was equal to or smaller than the size of the hybridization signal.

Negative controls were established on cultures of bone marrow aspirate specimens from 10 known negative patients. The probe specificity was confirmed by mapping back to metaphase nuclei. Positive controls used in this study were cases of MALT lymphoma with rearrangements involving 18q21 identified by conventional cytogenetics and FISH previously.[14]

Results

Histologic Findings

All eight cases of MALT-lymphoma had a diffuse growth pattern. Mitotic activity was low and areas of necrosis were not seen. The neoplastic cells were small with irregular nuclear contours and pale or monocytoid cytoplasm (Figure 1). Lymphoepithelial lesions were identified in a subset of cases but were not prominent. Two cases showed prominent plasmacytic differentiation.

All 14 diffuse large B-cell lymphomas cases had a diffuse pattern of growth (Figure 2). Twelve were centroblastic, one was immunoblastic and one could not be further subclassified. The latter neoplasm was composed of small noncleaved cells with a starry-sky pattern, a high mitotic index and numerous apoptotic cells, histologically mimicking Burkitt lymphoma. However, unlike Burkitt lymphoma, the proliferation index as assessed by MIB-1 (Ki-67) immunostaining was 85–90%, the neoplastic cells were positive for BCL-2, and there was no evidence of *c-myc* rearrangement identified by FISH. In all 14 cases of diffuse large B-cell lymphomas, there was no evidence of a component of low-grade MALT lymphoma.

Immunohistochemical Findings

The results of BCL-10 staining in eight MALT lymphoma and 14 diffuse large B-cell lymphoma cases are summarized in Table 1. In the MALT lymphoma group, BCL-10 was positive in seven neoplasms and negative in one. In the positive group, six neoplasms had a moderate nuclear and weaker cytoplasmic pattern (Figure 3) and one had a weak cytoplasmic pattern. In the diffuse large B-cell lymphomas group, BCL-10 was positive in 12 and negative in two neoplasms. In the positive group, 10 neoplasms had a weak to moderate cytoplasmic pattern, one had a weak cytoplasmic staining with a small subset of nuclei also weakly positive (Figure 4), and one had a moderate-to-strong nuclear and cytoplasmic pattern of staining.

The results for the p65 and p50 subunits of NF-κB are also summarized in Table 1. In the MALT lymphoma group, p65 ($n=8$) was positive with a cytoplasmic pattern in five (Figure 5) and negative

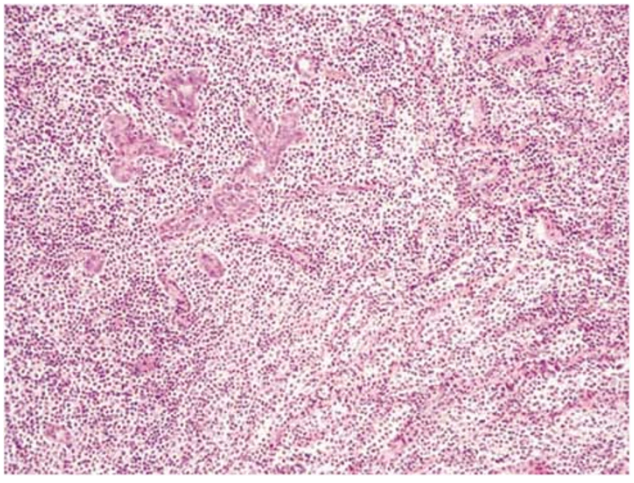

Figure 1 MALT lymphoma of breast. The neoplasm is composed predominantly of small cells, many of which had monocytoid cytoplasm (hematoxylin and eosin, ×200).

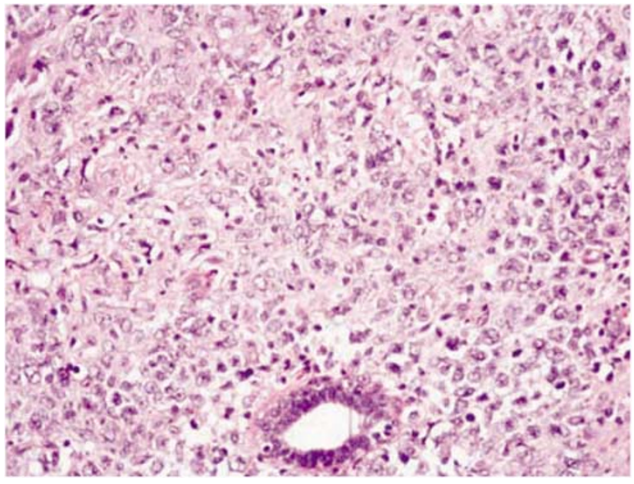

Figure 2 Diffuse large B-cell lymphoma of breast. The neoplasm is composed of large cells with one to several nucleoli (hematoxylin and eosin, ×400).

Table 1 Expression of BCL-10 and NF-κB p65 and p50, and FISH analysis of 22 MALT lymphomas and diffuse large B-cell lymphomas of the breast

Case No.	*Age*	*Gender*	*Diagnosis*	*BCL10*	*NF-κB P65*	*NF-κB P50*	*FISH*
1	61	Female	MALT-L	Neg	C	ND	Neg
2	80	Male	MALT-L	N/C	C	ND	Neg
3	69	Female	MALT-L	C	C	Neg	Neg
4	69	Female	MALT-L	N/C	C	ND	Neg
5	79	Female	MALT-L	N/C	C	C	Neg
6	62	Female	MALT-L	N/C	Neg	C	Neg
7	69	Female	MALT-L	N/C	Neg	C	Neg
8	51	Female	MALT-L	N/C	Neg	C	Neg
9	42	Female	DLBCL	C	C	Neg	Neg
10	30	Female	DLBCL	N/C*	C	C	Neg
11	70	Female	DLBCL	C	C	C	Neg
12	79	Female	DLBCL	C	C	C	Neg
13	56	Female	DLBCL	C	C	N/C	Neg
14	32	Female	DLBCL	C	ND	ND	Neg
15	65	Female	DLBCL	C	C	C	Neg
16	57	Female	DLBCL	C	ND	ND	Neg
17	32	Female	DLBCL	C	C	ND	Neg
18	57	Female	DLBCL	N/C	C	N/C	Neg
19	50	Female	DLBCL	C	C	ND	Neg
20	33	Female	DLBCL	C	ND	ND	Neg
21	51	Female	DLBCL	C	C	C	Neg
22	85	Female	DLBCL	Neg	C	ND	Neg

DLBCL, diffuse large B-cell lymphoma; MALT-L, extranodal marginal zone B-cell lymphoma of MALT; Neg, negative; C, cytoplasmic pattern; N/C, nuclear and cytoplasmic pattern; N/C*, nuclear (small subset) and cytoplasmic pattern; ND: not done.

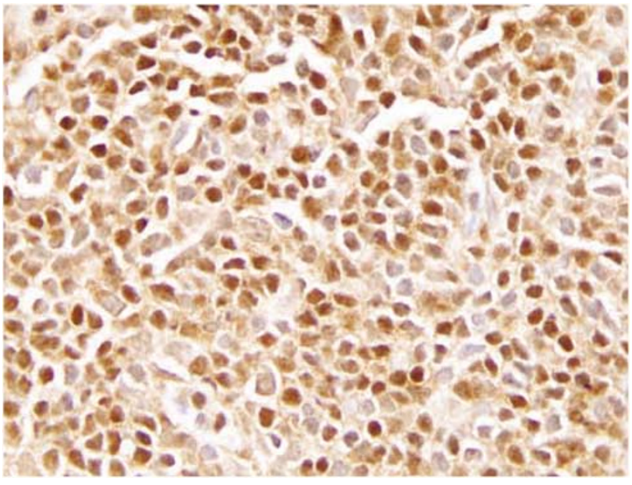

Figure 3 MALT lymphoma of breast. The neoplasm shows moderate nuclear and weaker cytoplasmic expression of BCL-10 (immunohistochemistry with hematoxylin counterstain, ×1000).

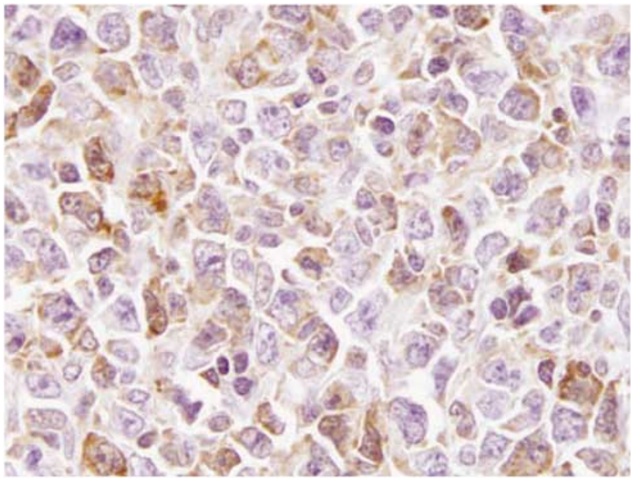

Figure 4 Diffuse large B-cell lymphoma of breast. The neoplasm shows weak cytoplasmic staining for BCL-10. In addition, in a small subset of cells weak nuclear staining is present (immunohistochemistry with hematoxylin counterstain, ×1000).

in three neoplasms, and p50 ($n=5$) was positive with a cytoplasmic pattern in four neoplasms (Figure 6) and negative in one. In the diffuse large B-cell lymphoma group, p65 ($n=11$) staining was cytoplasmic in all neoplasms assessed (Figure 7), and p50 ($n=8$) was nuclear and cytoplasmic in two (Figure 8), negative in one, and cytoplasmic in five neoplasms assessed.

FISH Analysis

Eight MALT lymphomas and 14 diffuse large B-cell lymphomas cases were assessed for *MALT1* gene rearrangements by FISH. There was no evidence of *MALT1* gene rearrangements in any of the neoplasms assessed.

Discussion

A number of chromosomal translocations have been identified in a subset of MALT lymphomas involving a variety of extranodal sites, including the t(11;18)(q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32), and t(3;14)(p14.1;q32).[3–5] These

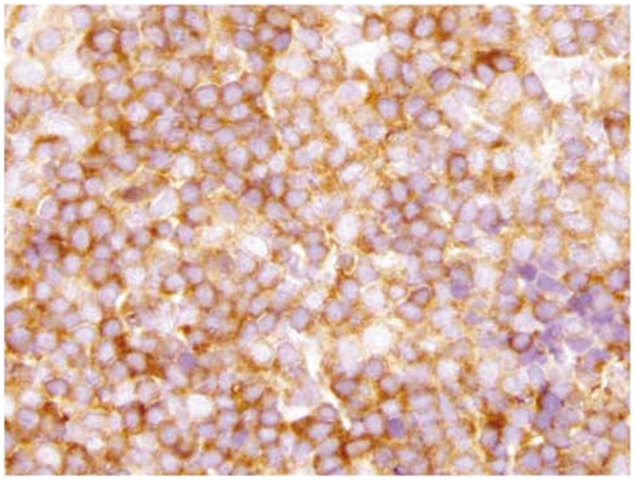

Figure 5 MALT lymphoma of breast. The neoplasm shows cytoplasmic staining for NF-κB p65 (immunohistochemistry with hematoxylin counterstain, ×1000).

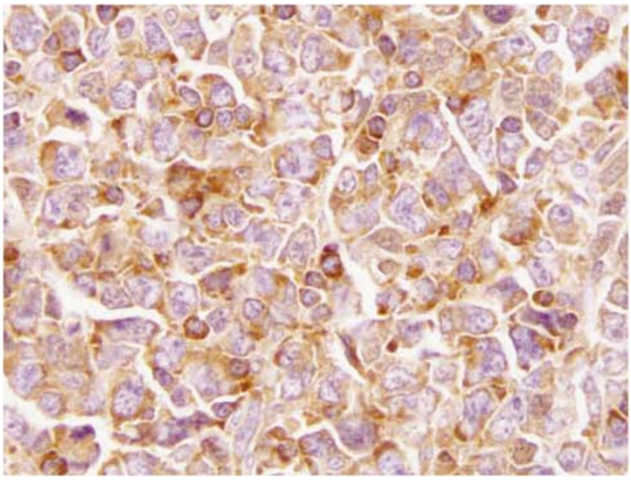

Figure 7 Diffuse large B-cell lymphoma of breast. The neoplasm shows cytoplasmic staining for NF-κB p65 (immunohistochemistry with hematoxylin counterstain, ×1000).

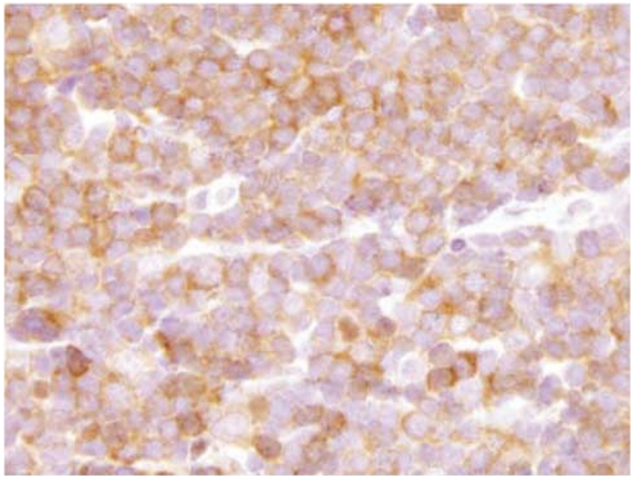

Figure 6 MALT lymphoma of breast. The neoplasm shows cytoplasmic staining for NF-κB p50 (immunohistochemistry with hematoxylin counterstain, ×1000).

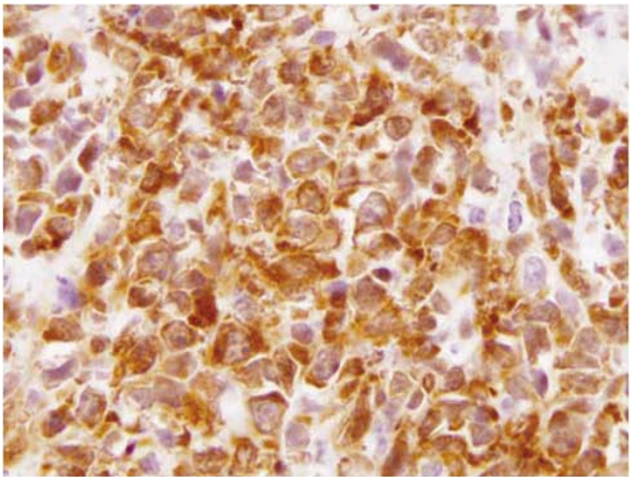

Figure 8 Diffuse large B-cell lymphoma of breast. The neoplasm shows nuclear (and cytoplasmic) staining for NF-κB p50 consistent with activation of the NF-κB pathway (immunohistochemistry with hematoxylin counterstain, ×1000).

abnormalities also appear to be mutually exclusive and their frequency correlates with anatomic site. Few MALT lymphomas of the breast, however, have been studied presumably because these neoplasms are rare. In a study of 252 MALT lymphomas by Streubel *et al*,[4] only five (2%) cases of breast MALT lymphoma were included. Another large study of 417 MALT lymphomas did not include any breast neoplasms.[3] The identification of only 10 cases of breast MALT lymphoma in our files over approximately 20 years further attests to the low frequency of breast MALT lymphomas relative to the frequency of MALT lymphomas involving other anatomic sites.

We performed FISH using a *MALT1* probe to study eight breast MALT lymphomas (with available unstained slides or blocks) for two of the MALT lymphoma-associated translocations. The FISH probe detects both the t(11;18) and t(14;18) involving the *MALT1* gene at 18q21. Our FISH results showed no evidence of *MALT1* gene rearrangements in all breast MALT lymphomas assessed. Combined with the results of Streubel *et al*[4] who studied five additional cases, 13 cases of breast MALT lymphoma assessed for the t(11;18) and t(14;18) were negative. Thus, *MALT1* gene rearrangements in breast MALT lymphomas are either absent or rare.

We also used BCL-10 immunostaining to indirectly assess for MALT lymphoma-associated translocations as has been reported by others.[7] BCL-10 is expressed primarily in the cytoplasm of normal B-cells, including germinal center and marginal zone B-cells.[15] In contrast, in MALT lymphomas BCL-10 immunostaining has been reported to show characteristic expression patterns

that correlate with the presence of specific translocations. In MALT lymphomas carrying the t(1;14), BCL-10 is predominantly and strongly expressed in the tumor cell nuclei. In MALT lymphomas with the t(11;18) or t(14;18), BCL-10 is moderately expressed in the nucleus or strongly expressed in the cytoplasm of tumor cells, respectively.[7,8,15,16] In this study, BCL-10 was positive with a moderate staining intensity in the nucleus and cytoplasm of six of eight (75%) MALT lymphomas. This result suggests the presence of the t(11;18) in these cases and is discordant with the FISH results. The explanation for this apparent discordance is uncertain, but others have reported moderate nuclear BCL-10 immunoreactivity in MALT lymphomas without the t(11;18).[14,16–19] More specifically, although moderate nuclear staining for BCL-10 is usually observed in MALT lymphomas with the t(11;18), up to 20–50% of MALT lymphomas without the t(11;18) also show moderate nuclear BCL-10 positivity. Thus, although BCL-10 immunostaining can be used as an initial screen for the t(11;18) in MALT lymphomas, the presence of BCL-10 nuclear expression should not be used as a surrogate for the presence of the t(11;18).

As shown by others, at least three of the chromosomal translocations identified in MALT lymphomas, the t(11;18), t(14;18), and t(1;14), result in activation of the downstream NF-κB pathway.[6,7] For this reason, we performed immunohistochemical staining to evaluate for expression of the p65 and p50 subunits of NF-κB. The transcription factor NF-κB is a dimer composed of members of the REL family of proteins that includes p65 (rel A), p50, p52, c-rel, and Rel-B.[20,21] In its inactive form, NF-κB is present in the cytoplasm of cells bound to an inhibitor, IκB. When an appropriate signal is received, NF-κB is translocated to the nucleus where it upregulates transcription of a number of genes. In many different tumor types, and in some gastric and ocular adnexal MALT lymphomas, evidence of NF-κB activation has been shown in a subset of cases.[17,19] As the p65 subunit is involved in many activated forms of NF-κB,[17,21] others have used immunohistochemical detection of nuclear p65 staining as evidence of NF-κB activation.[17] The p50 subunit of NF-κB is also present in mature B lymphocytes.[21] Thus, we assessed for expression of both NF-κB p65 and p50 in the eight breast MALT lymphomas in this study. In all cases, the staining pattern was only cytoplasmic or negative suggesting that NF-κB is inactive. These results further suggest that MALT lymphoma-associated translocations that are known to activate NF-κB are absent or rare in breast MALT lymphomas. However, using the methods employed, we cannot exclude the possibility that NF-κB activation occurs in breast MALT lymphomas, but does not involve either p65 or p50.

At other extranodal sites, a subset of diffuse large B-cell lymphomas has been shown to be associated with serologic evidence of *H. pylori* infection,[11] or coexistent with low-grade MALT lymphoma,[9,10] suggesting that these diffuse large B-cell lymphomas cases may originate from benign MALT tissue or represent transformation from MALT lymphoma. For these reasons, we also assessed cases of primary diffuse large B-cell lymphoma of the breast in this study. In all cases analyzed, there was no evidence of *MALT1* gene rearrangements. BCL-10 immunostaining showed that 12 of 14 cases assessed had weak cytoplasmic ($n=11$) or weak cytoplasmic and focally nuclear staining ($n=1$), concordant with the absence of *MALT1* gene rearrangements. NF-κB p65 showed cytoplasmic staining in all cases assessed, however, p50 staining was nuclear consistent with NF-κB activation in two of eight cases of DLBCL studied. The BCL-10 and NF-κB p50 results differ from that of the breast MALT lymphomas we analyzed indicating that these neoplasms have differences in their pathogenesis.

One of 14 (7%) breast diffuse large B-cell lymphomas assessed had moderate to strong nuclear and cytoplasmic BCL-10 immunostaining. Strong nuclear BCL-10 expression is thought to correlate strongly with the presence of the t(1;14),[7] and thus this case may carry this translocation. However, as our laboratory does not have a probe for the BCL-10 locus, we cannot confirm this finding.

In summary, the FISH and NF-κB immunostaining data suggest that *MALT1* gene translocations and NF-κB activation involving p65 and p50 are absent or rare in cases of primary breast MALT lymphoma. BCL-10 immunostaining in breast MALT lymphomas is discordant with these results, but nuclear BCL-10 staining has been reported in extra-mammary MALT lymphomas without the t(11;18) in other studies.[14,17–19] Thus, our results support those of others and suggest that moderate nuclear BCL-10 immunostaining overestimates the percentage of neoplasms that carry *MALT1* gene rearrangements. The BCL-10 and NF-κB data in primary breast diffuse large B-cell lymphomas shows that this group is heterogeneous, with most cases showing weak cytoplasmic BCL-10 staining and a subset of cases showing evidence of NF-κB activation, unlike breast MALT lymphomas.

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