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FOXP1 status in splenic marginal zone lymphoma: a fluorescence *in situ* hybridization and immunohistochemistry approach

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Summary. Splenic marginal zone lymphoma (SMZL) is a well-recognized entity in which chromosomal aberrations seem to be potential markers in diagnosis, prognosis and disease monitoring.

FOXP1 is a transcriptional regulator of B lymphopoiesis that is deregulated in some types of NHL. Translocation t(3;14)(p14;q32) has been described in marginal zone lymphomas but few series have studied *FOXP1* involvement in SMZL. We performed cytogenetic, fluorescence *in situ* hybridization (FISH) and immunohistochemical (IHC) studies in a series of 36 patients in order to study the status of *FOXP1* in this entity.

According to our results, *FOXP1* is not rearranged in SMZL, although we were able to demonstrate gains of *FOXP1* gene due to trisomy 3/3p by FISH. FOXP1 protein expression seemed to be not related to any aberration and IHC studies are not conclusive.

Key words: *FOXP1*, FISH, IHC, SMZL

Introduction

The *Forkhead box protein P1 (FOXP1)* gene, localized at chromosome 3p14 region, exhibits loss of heterozigosity (LOH) in human cancer and therefore is considered a new candidate tumor suppressor gene that is down regulated in solid tumors. However, the role of *FOXP1* in hematopoietic malignancies has not been extensively described (Banham et al., 2001). Overexpression of *FOXP1* has been observed in cases of diffuse large B-cell lymphoma (DLBCL) and a high expression of FOXP1 protein has been associated with non-germinal center DLBCL type with a poor outcome (Barrans et al., 2004; Banham et al., 2005). However, the potential mechanisms of deregulation of *FOXP1* in non-Hodgkin lymphomas (NHL) are unclear, but in some cases cytogenetic changes have been reported as the underlying mechanism (Haralambieva et al., 2005; Streubel et al., 2005; Wlodarska et al., 2005; Fenton et al., 2006).

Recently, translocation t(3;14)(p14;q32) involving *FOXP1* gene and heavy chain immunoglobulin gene *(IGH)* has been described in mucosa associated lymphoid tissue (MALT) and extranodal DLBCL lymphomas (Haralambieva et al., 2005; Streubel et al., 2005; Wlodarska et al., 2005; Fenton et al., 2006). Large series of MALT lymphomas have been investigated by a two-color fluorescence *in situ* hybridization (FISH) assay. The frequency of positive cases for the translocation (10%) was site dependent and lymphomas harboring this rearrangement showed additional chromosomal aberrations such as trisomy 3 (Streubel et al., 2005).

Some studies postulated that in DLBCL overexpression of FOXP1 protein does not occur due to gene translocation (Wlodarska et al., 2005; Barrans et al., 2007).

On the other hand, little is known regarding the role of *FOXP1* gene in splenic marginal zone lymphoma (SMZL). SMZL is a well-recognized entity in which the

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clinical, morphological, immunophenotypical and histological characteristics are well established (Mollejo et al., 1995; Jaffe et al., 2001; Matutes et al., 2007), and the associated cytogenetic abnormalities are expected to be helpful in the differential diagnosis with other types of lymphomas (Dierlamm et al., 2000; Hernández et al., 2001; Solé et al., 2001; Aamot et al., 2005; Baró et al., 2008).

Rearrangements involving *IGH* locus, a common feature in NHL, have been rarely described in SMZL (Solé et al., 2000; Baró et al., 2006; Martín-Subero et al., 2007; Remstein et al., 2007). Regarding t(3;14) (p14;q32), only eight cases of SMZL were previously studied and all of them were considered negative for translocation (Streubel et al., 2005).

The aim of this study was to investigate the status of *FOXP1* gene by FISH in a series of 36 well-defined SMZL cases and to correlate it with FOXP1 immunohistochemical expression.

Materials and methods

Patients

Thirty-six patients diagnosed with SMZL according to WHO criteria for this entity (Jaffe et al., 2001) were included in the study. Seventeen of them (cases 1, 3, 8, 12, 13, 16, 17, 20, 21, 22, 23, 24, 26, 27, 28 and 29) have been previously studied to attempt to establish a comprehensive cytogenetic analysis in SMZL (Solé et al., 2001; Baró et al., 2008). Patients were referred from different hospitals belonging to the Spanish Cytogenetic Working Group (GCECGH, AEHH) and from the *Red de Grupos de Linfomas* (G03/179).

Conventional banding cytogenetics and fluorescence in situ hybridization (FISH) studies

G-banding analyses were carried out according to standard procedures from Carnoy fixed cells (12 peripheral bloods, seven bone marrow and 17 spleens). Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN) (Shaffer and Tommerup, 2005).

FISH was performed in fixed cells from peripheral blood (n=12), bone marrow (n=7) and in paraffin-embedded spleen samples (n=7) following standard procedures. In ten of 17 spleen sections, FISH results were not available due to the poor quality of the hybridization. In such cases (n=10), Carnoy fixed cells of these spleens were used (Table 1). A *FOXP1* (3p14) dual color break apart non-commercial translocation probe was designed to detect translocations in this gene. The probe consisted of two bacterial artificial chromosome (BAC) clones directly labeled using nick translation: BAC RP11-713J7 labeled in green and located at 5' of the gene and BAC RP11-79P21 labeled in red and located at 3' of the gene. All the previously described breakpoints of *FOXP1* are located at 90Kb downstream of the gene, so that the dual color designed probe could detect all previously described translocations of *FOXP1*. In this regard, Wlodarska et al. also used these two BACs in their FISH DNA probes panel to analyze *FOXP1* rearrangements (Wlodarska et al., 2005). In all cases, a minimum of 100 nuclei were examined and metaphases were studied when it was possible.

Ten peripheral blood samples from healthy donors were used to assess the cut-off in cell suspensions. The cut-off value for this probe was calculated as the mean percentage of cells with a false-positive signal constellation plus three standard deviations. Two hundred nuclei were evaluated in each negative control and the cut-off values for the *FOXP1* rearrangement and for gains (three copies of *FOXP1* gene) were 1% and 3% respectively. Five tonsil samples from healthy donors were used as negative controls in paraffin-embedded tissues. In these cases, the cut-off values obtained were 2% for the *FOXP1* rearrangement and 10% for gains of *FOXP1*. One hundred nuclei were scored in each paraffin-embedded control case.

FOXP1 protein immunohistochemistry (IHC)

FOXP1 protein IHC was carried out in 17 patients in whom sections of the spleen were available (Table 1). The FOXP1 antibody, clone JC12 (Banham et al., 2001), was kindly provided by Dr. Alison Banham (Nuffield Department of Clinical Laboratory Sciences, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom). IHC was performed on formalin-fixed paraffin-embedded tissue sections. Briefly, paraffin sections on silane-coated slides were developed in a fully automated immunostainer (Bond Max, Vision Biosystems, Mount Waverley, Australia). High pH retrieval in Bond ER1 Buffer solution (Vision Biosystems, Mount Waverley, Australia) was performed for 20', followed by 30' incubation with the primary antibody (1:80) and 30' of Bond Refine Polymer (Vision Biosystems, Mount Waverley, Australia). 5'-3'Diaminobenzidne (DAB) was used for 10' as a chromogen. The cases were considered positive when more than 30% of atypical cells were positive. Intensity of FOXP1 was scored as weak, moderate or strong (Table 1).

Results

No rearrangements of *FOXP1* were found in any case of SMZL. Three copies of the gene were detected in seven of 36 (19,5%) patients. Gains of *FOXP1* were due to the presence of extra copies of whole chromosome 3 (5 cases) or due to partial trisomy of 3p by unbalanced translocations (2 cases). In one patient (case 3), discordant G-banding and FISH results were found: although a trisomy 3 was detected by conventional banding cytogenetics (only in two out of 30 metaphases with poor morphology), FISH analysis could not confirm

Table 1. Cytogenetic, FISH and IHC results in a series of 36 SMZL.

Case	TS	Conventional Karyotype	FISH Results FOXP1	IHC Results	Spleen Pattern
1	PB	44-89,XX, +3,der(3)t(3;8)(q27;q24), del(6)(q15), der(6)t(6;8) (q23;q24), del(7)(q31q36), der(17;18)(q10;q10), +18,i(18) (q10)[cp4]	28% three copies		
2	PB	46,XX,t(1;3)(q25;p13),del(2)(p23),add(19)(p13)[2]/45,XX,t(1;3)(q25;p13), del(2)(p23), add(13)(q34), add(14)(q32),-22[1]/46,XX,t(1;3) (q25;p13), add(19)(13)[1]/ 46, XXadd(2)(q37), [1]/46,XX,del(X) (q22)[1]/46,XX[14]	25% three copies		
3	BM	48-49,XX,+3,+5,der(9),-10,-12,add(13)(q34),+2mar[cp2]/46,XX[28]	Normal		
4	PB	47,XX,t(3;18)(q11;p11),+18,der(18)t(3;18)(q11;p11)[2]	Normal		
5	PB	47-49,X,-X,+3,del(6)(q23),+7,+9,der(9)t(X;9)(?;q34),+18[cp6]	33% three copies		
6	BM	45,XX,t(3;4;14)(p21;q34;q32),-8,t(8;12)(q11;p11)[3]/45,XX, t(3;4;14)(p21;q34;q32), -12,der(22)t(12;22)(q11;q13)[3]/46,XX, t(3;4;14)(p21;q34;q32),del(12)(q11)[2]	8% three copies		
7	BM	46,XX,del(7)(q22),der(13)t(3;13)(q21;q14)[2]	Normal		
8	spleen	46-47,XY,der(6)t(3;6)(q11;q11),del(7)(q22),der(19)t(12;19)(q11;q13), +mar(12)[cp4]	Normal	strong expression	prominent red pulp involvement
9	spleen	48,XX,+3,+12[20]	19% three copies	weak expression	micronodular
10	BM	47-48,XX,dup(3)(q11q27),+7,del(7)(q22q34),del(7)(q22q34),+11[cp2]	Normal		
11	BM	47-49,X,-X,+3,der(3)t(3;8)(3pter→3q11::8q24→8qter),+7,del(7) (q32q35) der(8)t(3;8)(3?q::8p11→8q22::3?q),t(9;14)(p13;q32), t(14;19)(q32;q13),+mar(11),+r(1)(p36q44)[cp4]	39% three copies		
12	PB	46,XY,der(6)t(3;6)(q13;p25),add(17)(p13),add(19)(q13)[cp2]	Normal		
13	PB	48,XY,+3,del(3)(q27),-6,inv(12)(p13q21),+18,+mar(2)[cp2]	64.5% three copies		
14	PB	46,XY,inv(3)(p13q26),del(7)(q22q32),del(10)(q24q26),del(11)(q21q23)[2]	Normal		
15	PB	45-47,XY,del(3)(p23),der(7)t(7;9;13)(7p22→7q32::9q22→9q34::13q14→ 13qter), del(9)(q22),der(9)t(9;15)(q34;q15),del(13)(q14),- 15,der(17)t(5;17) (q22;p13), der(22)t(20;22)(q11;p11)[cp4]	Normal		
16	PB	44-45,XY,t(2;7)(p12;q22),der(8)t(8;21)(q22;q11),del(14)(q22)[cp2]	Normal		
17	spleen	46,XY,del(7)(q32)[1]/46,XY[19]	Normal	no expression	slight lymphoid tissue increase
18	PB	46,XY,t(2;12)(p12;q24),del(6)(q21),del(6)(q23),del(17)(p13)[5]/46,XY[25]	Normal		
19	PB	46,XX,del(7)(q32),del(10)(p21q11)[20]	Normal		
20	spleen	46,XX,del (7)(q22)[17]/46,XX[3]	Normal	moderate expression	micronodular
21	ξspleen	46,XX[20]	Normal	weak expression	micronodular
22	spleen	46,XX,del(7)(q32)[6]/46,XX[9]	Normal	strong expression	prominent red pulp involvement
23	ξspleen	46,XX,del(7)(q22)[15]	Normal	no expression	slight lymphoid tissue increase
24	BM	47,XX,+12[4]/46,XX[16]	Normal		
25	ξspleen	46,XX[20]	Normal	strong expression	prominent red pulp involvement
26	PB	44-47,XY,t(1;6)(p34;p23),+2,del(2)(q21),der(2)t(2;21)(p12;q11),+8, dic(8;15)(q24;q26),del(11)(q11),i(17)(q10),+mar(2),+mar(Y)[cp9]	Normal		
27	ξspleen	46,XX[20]	Normal	moderate expression	micronodular
28	BM	43-44,XY,del(7)(q21),-9,t(10;15)(q22;q22),der(13;14)(q10;q10),der (13;18) (q10;q10),der(17)t(9;17)(?;p13)[cp4]	Normal		
29	spleen	42-48,XX,del(2)(q23),der(17)t(5;17)(?;p13),+dmin(1),+dmin(3)[cp4]	Normal	weak expression	micronodular
30	spleen	46,XY[20]	Normal	strong expression	micronodular
31	spleen	46,XY,del(7)(q32)[6]/46,XY[1]	Normal	strong expression	prominent red pulp involvement
32	spleen	46,XY[30]	Normal	no expression	micronodular
33	ξspleen	46,XX,del(7)(q32),add(19)(q13)[10]/46,XX[10]	Normal	weak expression	micronodular
34	ξspleen	46,XY[10]	Normal	moderate expression	micronodular
35	ξspleen	46,XX[20]	Normal	moderate expression	micronodular
36	spleen	46,XX,i(12)(q10)[5]/46,XX[15]	Normal	moderate expression	micronodular

TS: tissue sample; PB: peripheral blood; BM: bone marrow; spleen: suspension cells; ξspleen: Paraffin-embedded tissue.

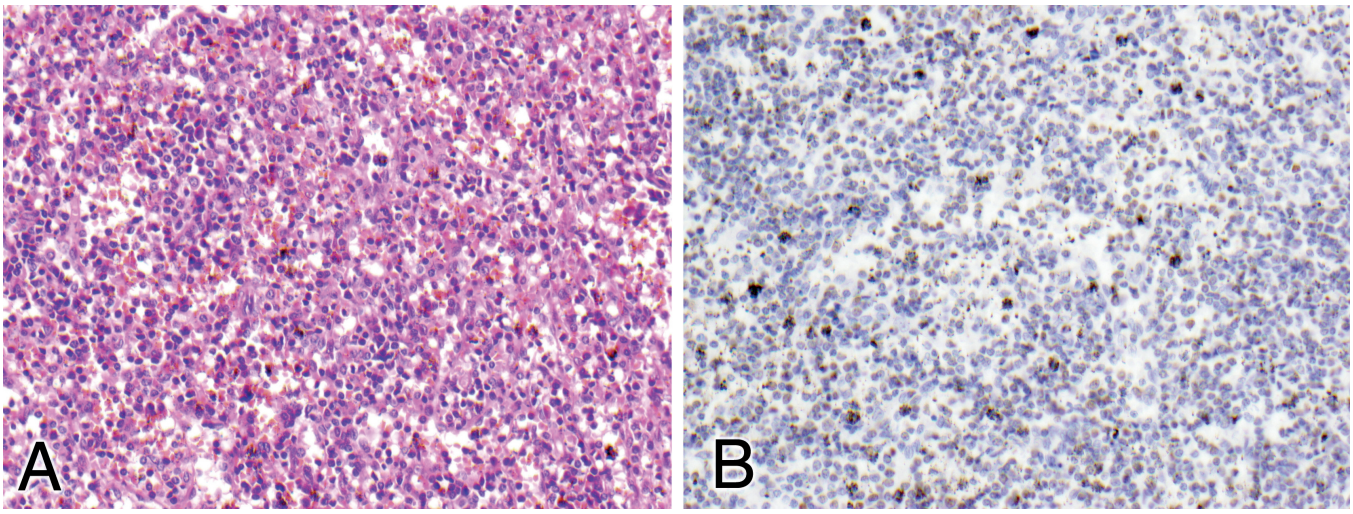

Fig. 1. Hematoxilin-eosin section **(A)** and FOXP1 IHQ **(B)** of the same lymphoid follicle of patient 8 at 20. x 200

this abnormality (Table 1).

IHC studies were performed in 17 out of 36 patients, in which histological spleen sections were available. Fourteen out of the 17 cases expressed FOXP1 protein, having strong and uniform expression in five cases (patients 22, 8, 25, 30 and 31). It is remarkable that three of them (patients 22, 8, and 31) presented a deletion of 7q associated with a prominent involvement of the splenic red pulp (Fig. 1). Cases 17 and 23, also with 7q deletion, only had a light increase of splenic lymphoid tissue and in those conditions IHC analysis could not detect FOXP1 expression. On the other hand, a patient with three copies of *FOXP1* detected by FISH (case 9) presented weak expression of the protein.

Unfortunately, splenectomy specimens of the remaining patients with gains of FOXP1 were not available (cases 1, 2, 5, 6, 11 and 13) and it was not possible to establish a correlation between *FOXP1* gains by FISH and FOXP1 expression results in SMZL.

Discussion

There is more than one mechanism of *FOXP1* deregulation in NHL, because a high expression of this gene is not necessarily due to the presence of rearrangement events. In the literature, deregulation of *FOXP1* has been referred to in cases with gains of chromosome 3, and this aberration was related to strong FOXP1 protein expression, suggesting an association between the occurrence of extra copies of *FOXP1* and aberrant expression of its protein (Haralambieva et al., 2005). Of note, trisomy 3 is one of the most common aberrations in SMZL (Dierlamm et al., 2000; Hernández et al., 2001; Solé et al., 2001; Aamot et al., 2005; Baró et al., 2008) although t(3;14)(p14;q32) has not been detected in this entity (Streubel et al., 2005). Some cases of NHL present translocations that could be masked due to the complexity of the karyotypes or due to the small size of the involved regions (Gozzetti et al., 2002; Gazzo et al., 2005; Baró et al., 2006). In these cases, FISH analyses could be helpful to detect or confirm successful chromosomal aberrations. Although *FOXP1* was not rearranged in the present series, three copies of this gene due to gains of chromosome 3 or 3p were observed.

We could not analyze the relationship between gains of chromosome 3/3p and FOXP1 protein expression by IHC in all cases because spleen sections were not available. Only one patient had both analyses, but there was no correlation because FOXP1 protein was weakly expressed and FISH showed three copies of the gene. In reference to this point, recent studies have reported the existence of FOXP1 isoforms in DLBCL that anti-FOXP1 (JC12) monoclonal antibody cannot distinguish (Brown et al., 2008). This could explain the discordance between IHC and FISH results in our case.

Deletion of 7q is considered a characteristic aberration of SMZL (Dierlamm et al., 2000; Hernández et al., 2001; Solé et al., 2001; Aamot et al., 2005; Baró et al., 2008). In this study, we found three patients with chromosome 7q deletion and a prominent involvement of the splenic red pulp. Moreover, cases with these features showed strong expression of FOXP1 protein. However, as the number of cases showing these two characteristics was low, we could not suggest any relationship.

The present series is the largest reported until now that has studied the involvement of *FOXP1* in SMZL. Large series of this entity with histological spleen sections available are needed to determine the relationship between FOXP1 expression and gains of 3/3p detected by FISH. In addition, further studies with patients presenting a prominent involvement of splenic red pulp and 7q deletion are needed to demonstrate or discard their association with strong expression of

FOXP1 protein.

Although *FOXP1* takes part in early B cell development transcriptional regulation (Fuxa and Skok, 2007) and is probably affected in some NHL, we could discard an involvement of this gene due to t(3;14)(p14;q32) in SMZL. However, other genes located in chromosome 3 have to be considered in the study of SMZL due to the high implication of this chromosome in this disease.

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