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TO THE EDITOR:

First description of the t(3;17)(q27;q21)/*IGF2BP2::LSM12* translocation in marginal zone lymphoma

Ramón Diez-Feijóo,[1,2,*] Concepción Fernández-Rodríguez,[2,3,*] Marta Lafuente,[2] Nieves García-Gisbert,[2] Ana Ferrer,[3,4] Luis Colomo,[3,4] Marta Salido,[3,4,†] and Antonio Salar[1,2,*,†]

[1]Department of Hematology, Hospital del Mar, Barcelona, Spain; [2]Group of Applied Clinical Research in Hematology, Cancer Research Program, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain; [3]Department of Pathology, Hospital del Mar, Barcelona, Spain; and [4]Group of Translational Research on Hematological Neoplasms, Cancer Research Program, IMIM, Barcelona, Spain

Marginal zone lymphoma (MZL) is a rare group of indolent non-Hodgkin lymphomas that originate from the marginal zone of lymphoid follicles.[1] Their diagnosis remains difficult and in many cases is finally performed by the exclusion of other low-grade B-cell lymphomas. Cytogenetically, gains of chromosomes 3 and 18 have been described in all subtypes of MZLs.[2] Specifically, extranodal lymphoma of the mucosa-associated lymphoid tissue is characterized by the occurrence of different translocations [t(11;18)(q21;q21), t(14;18)(q32;q21), and t(1;14)(p22;q32)].[3] The deletion of 7q is the most frequent abnormality in primary splenic MZL (30%-40% of patients), and trisomy of chromosomes 3/3q is the most recurrent gain. Cytogenetics in nodal MZLs (NMZLs) is not well defined.[4] Molecularly, splenic MZL and NMZL have a common genetic background, characterized by mutations in *NOTCH*, *KLF2*, and NF-κB genes.[5-8] Mucosa-associated lymphoid tissue lymphomas show a heterogeneous genetic landscape in which many genes, such as *TNFAIP3*, *KMT2C*, *KMT2D*, *CREBBP*, *TET2*, *SPEN*, *LRP1B*, *PRDM1*, and *EP300*, may be involved.[9]

Here, we describe a new gene fusion *IGF2BP2::LSM12* in 2 patients with MZL and translocation t(3;17)(q27;q21) in the karyotype. To our knowledge, this is the first time that this genetic alteration has been reported in cancer.

Cytogenetic tests on bone marrow (BM), peripheral blood (PB), and lymph node (LN) were performed according to the standard methods used in our laboratory. Fluorescence in situ hybridization (FISH) study using clones from human 32K bacterial artificial chromosome rearray library (BACPAC Genomics, Richmond, CA) was applied to confirm *IGF2BP2::LSM12* fusion in metaphases from altered karyotypes (supplemental Figure 1). Cytoscan 750K Array Kit cytogenetic solution (Affymetrix, ThermoFisher) was used to study genetic gain, loss, and copy neutral loss of heterozygosity following the current recommendations. Optical genome mapping (OGM) was performed with the rare variant pipeline included in Bionano Solve software (version 3.5) (Bionano Genomics, San Diego, CA) and visualized in Bionano Access software (version 1.6) to identify structural variants and large copy number variants. Targeted next-generation sequencing (NGS) was performed on DNA extracted from the PB mononuclear cells or the LN. Gene libraries were prepared with a QIAseq Targeted DNA Custom Panel (Qiagen, Hilden, Germany) covering the full coding region of 15 genes involved in lymphoid malignancies (supplemental Table 1) and were sequenced with MiSeq (Illumina, San Diego, CA). Single nucleotide variants and insertions/deletions were assessed with a sensitivity of 2% of variant allele frequency. Whole-genome sequencing (WGS) was performed using DNA from BM of patient 1, allowing the analysis of single nucleotide variants, insertions/deletions, copy number variants, and rearrangements (Novogene Co, United Kingdom). All the alterations reported were reviewed using Integrative Genomics Viewer software (Broad Institute).

The full-text version of this article contains a data supplement.

Table 1. Comparative table of the clinical and biological characteristics of the 2 patients

	Patient 1	Patient 2
Age, y	47	76
Sex	Male	Female
Eastern Cooperative Oncology Group scale	0	0
B symptoms	No	No
Lymph nodes affected	2 sides of the diaphragm	2 sides of the diaphragm
Splenomegaly	No	No
Extranodal involvement	No	Gastrointestinal infiltration
PB expression	Yes	Yes
BM involvement	Yes	Yes
Ann Arbor stage	IV	IV
Hemoglobin (g/L)	116	120
Platelets ($\times 10^9$/L)	60	234
Leucocytes		
Global count ($\times 10^9$/L)	6.86	12.7
Neutrophils ($\times 10^9$/L)	1.5	4.2
Lymphocytes ($\times 10^9$/L)	4.92	7.8
Monoclonal gammopathy	No	IgM
Increased lactate dehydrogenase	No	No
Increased β2 microglobulin	No	No
HIV	Negative	Negative
HBV; HCV	Positive HB core antibody, negative HB surface antigen; HCV negative	Positive HB core antibody, negative HB surface antigen; HCV negative
Immunophenotype	CD19^{++}, CD20^{++}, CD79b$^+$, CD23$^+$, CD25$^+$, CD5$^+$, BCL2^{+++}, kappa restriction CD10$^-$, CD11c$^-$, CD103$^-$, CD123$^-$, CD200$^-$, BCL6$^-$, cyclin D1$^-$, SOX11$^-$	CD19^{++}, CD20^{++}, CD79b$^+$, CD5$^-$, CD11c$^+$, BCL2^{+++}, kappa restriction CD10$^-$, CD23$^-$, CD103$^-$, CD123$^-$, CD200$^-$, cyclin D1$^-$
Ki67 (%)	10-20	5
Cytogenetics		
Karyotype	46,XY,t(3;17)(q27;q21)[10]/46,XY[10]	46,XX,t(3;17)(q27;q21)[15]/46,XX[5]
FISH, *IGF2BP2:LSM12*	Positive in 60% of the nuclei	Positive in 58% of the nuclei
FISH, *IGH:CCND1*	Negative	Negative
FISH, *BCL6* (3q27) SPLIT	Negative	Negative
Single nucleotide polymorphism array	No copy number alterations or loss of heterozygosis	No copy number alterations or loss of heterozygosis
OGM	Not done	*IGF2BP2::LSM12*
MYD88	Not mutated	Not mutated
CXCR4	*CXCR4* Ser341PhefsTer3 mutation	Not mutated
WGS	*CXCR4* Ser341PhefsTer3 mutation *IGF2BP2::LSM12*	Not done

HBV, hepatitis B virus; HCV, hepatitis C virus.

The first patient was a 45-year-old man who presented with a 4-month history of peripheral lymphadenopathy. Physical examination revealed bilateral cervical, axillary and inguinal enlarged LNs. Laboratory investigations showed a hemoglobin level of 116 g/L, leukocyte count of 6.86×10^9/L (neutrophils, 1.5×10^9/L; lymphocytes, 4.92×10^9/L), and platelet count of 60×10^9/L. A positron emission tomography scan revealed increased metabolic uptake in LNs at cervical, axillary, and inguinal regions. A PB smear examination identified atypical lymphocytes (6%). BM aspiration and biopsy showed 90% infiltration of atypical small lymphocytes.

Flow cytometry (FC) analysis on BM was consistent with the diagnosis of MZL (Table 1). Karyotype of the BM revealed a single alteration t(3;17)(q27;q21). An excisional biopsy of an inguinal LN was performed, and a vaguely nodular infiltration by small lymphoid cells effacing the LN architecture was found. The immunophenotype was equivalent to that observed in the BM. Cyclin D1, SOX11, and in situ hybridization for Epstein-Barr virus were negative and proliferative index determined by Ki67 immunostaining was 10% to 20%. Cytogenetic analysis of LN cells also showed t(3;17)(q27;q21). NGS lymphoid custom panel showed the
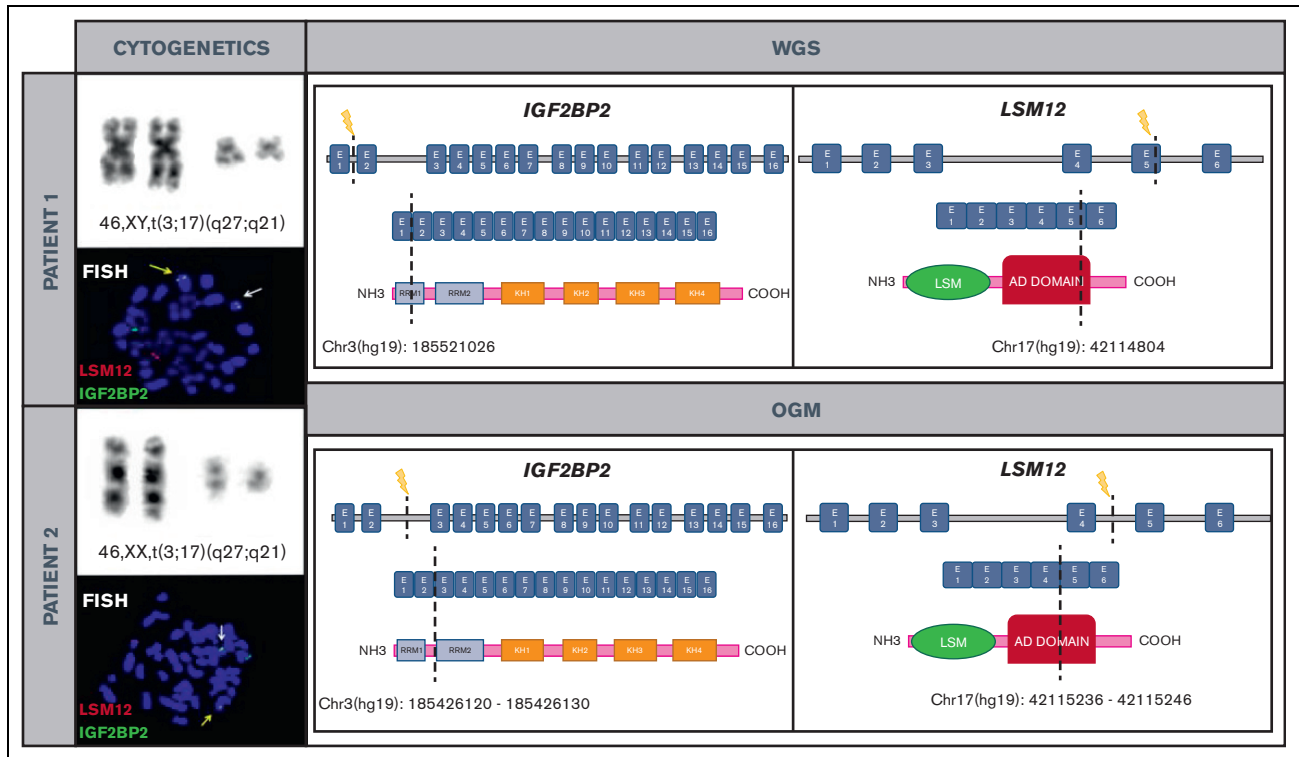
Figure 1. Cytogenetic and molecular characterization of t(3;17)(q27;q21)/*IGF2BP2::LSM12* in both patients. Chromosomes and metaphase-FISH of both patients show t(3;17)(q27;q21)/*IGF2BP2::LSM12* fusion (left). Dashed line indicates the DNA and domain structure breakpoints (*LSM12*: NM_152344 and *IGF2BP2*: NM_006548.6) revealed after WGS and OGM in both patients. Breakpoints at *IGF2BP2* affect RNA recognition motif 1. The RNA recognition motifs have high affinity for RNA, determining the binding capacities of the RNA-binding proteins (RBPs) to RNA, play a central role in the stability of *IGF2BP*-RNA complexes, and coordinate the interactions between the complex and other RBPs. Breakpoints at *LSM12* affect anticodon binding domain (AD). Its function consists of binding the anticodon of transfer RNA (right). COOH, carboxylic acid; E, exon; NH$_3$, ammonia.

pathogenic *CXCR4* frameshift mutation p.(Ser341PhefsTer3), with a variant allele frequency of 20.9%. The diagnosis of NMZL was established based on integration of the clinical, morphological, immunophenotypic, and genetic data.[10] To better characterize t(3;17)(q27;q21), we performed WGS that identified a rearrangement between *IGF2BP2* (cytogenetic location 3q27.2) and *LSM12* (cytogenetic location 17q21.31) (supplemental Figure 2). These findings were later confirmed by FISH (Figure 1). The patient was treated with rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for 6 cycles and achieved metabolic complete remission with negative minimal residual disease measured by FC, both in PB and BM.[11]

We reviewed the cytogenetic database of MZLs from our institution and identified another patient with t(3;17)(q27;q21) detected in PB. This patient was a 76-year-old woman who was referred to our hematology department in 2016 because of lymphocytosis. She did not have any medical history of interest and was asymptomatic. Physical examination was unremarkable. Laboratory investigations showed a hemoglobin level of 120 g/L, a leukocyte count of 12.79×10^9/L (neutrophils, 4.2×10^9/L and lymphocytes, 7.8×10^9/L), and a platelet count of 234×10^9/L. The PB smear analysis showed 52% atypical small lymphocytes, and immunophenotype determined by FC was consistent with the diagnosis of MZL (Table 1). Karyotype of the PB showed the t(3;17)(q27;q21), and *IGF2BP2::LSM12* fusion gene was confirmed by FISH. OGM

was performed to clarify specific breakpoints involved in *IGF2BP2::LSM12* fusion (Figure 1; supplemental Figure 3). NGS lymphoid custom panel did not detect mutations. BM biopsy showed 20% infiltration of atypical small lymphocytes with the same immunophenotype as described for the blood; cyclin D1 and SOX11 were negative, and proliferative index determined by Ki-67 immunostaining was 5%. Body computed tomography showed slightly increased LN on both sides of the diaphragm (size, <1.5 cm). The diagnosis of monoclonal B-cell lymphocytosis of marginal zone origin was established. The patient followed a watch-and-wait strategy, but 5 years after diagnosis, a computed tomography scan showed nodal progression without splenomegaly. An upper gastroduodenal endoscopy showed diffuse duodenal infiltration by small lymphoid cells with histology and immunophenotype consistent with MZL.

Here, we describe 2 patients with MZL with a novel genetic alteration t(3;17)(q27;q21)/*IGF2BP2::LSM12*. From the clinical perspective, both patients had disseminated LN involvement, BM infiltration, and PB expression. Clinical behavior was indolent, with slow growing lymphadenopathy in both patients. To our knowledge, this is the first time that a pathogenic relationship between *IGF2BP2*, *LSM12*, and MZL has been reported.[5,12-17] The insulin-like growth factor 2 messenger RBPs (*IGF2BP1*, *IGF2BP2*, and *IGF2BP3*) belong to a family of RBPs that modulate important aspects of cell function in cancer biology, such as cell polarization,

migration, metabolism, proliferation, and differentiation.[18] *IGF2BP2* has been reported as an oncogene because its overexpression has been associated with aggressive phenotype and poor prognosis in various solid tumors, acute myeloid leukemia, and diffuse large B-cell lymphomas.[19-21] *LSM12* is also an RBP that interacts with target messenger RNA to regulate gene posttranscriptional expression, which could affect the expression and function of proto-oncogenes and tumor suppressor genes.[22] Its implication in oncogenesis has been minimally described. *LSM12* has been identified as a fusion partner with *BRCA1* in a pantumor survey of 346 cases of BRCA-associated tumors in males.[23] In colorectal cancer, *LSM12* overexpression negatively correlates with tumor immune infiltration levels, which may promote colorectal cancer transfer.[24] In pancreatic adenocarcinoma, *LSM12* seems to be downregulated according to a recent study.[25]

In summary, we report a novel genetic alteration t(3;17)(q27;q21)/ *IGF2BP2::LSM12* in 2 patients with MZL. Further investigations are needed to better understand the implications of this genetic alteration in lymphomagenesis.

Contribution: R.D.-F. performed the research, analyzed and interpreted the clinical and biological results, and wrote the manuscript; C.F.-R. performed next-generation sequencing, analyzed the NGS and WGS data, and wrote the manuscript; M.L. and N.G.-G. collected and analyzed the clinical and biological data; A.F. and L.C. performed the cytologic, immunophenotypic, and histologic diagnostic; A.S. and M.S. designed the research, performed the research, analyzed and interpreted the results, and wrote the manuscript; and all authors reviewed and approved the final version of the manuscript.

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ORCID profiles: N.G.-G., 0000-0002-8185-9786; A.F., 0000-0002-3381-9472; L.C., 0000-0001-5236-5085; M.S., 0000-0001-9988-5977; A.S., 0000-0002-4652-4825.

Correspondence: Antonio Salar, Department of Hematology, Hospital del Mar, Passeig Maritim, 25-29, 08003 Barcelona, Spain; email: asalar@parcdesalutmar.cat.

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