

## Absence of *malt1* translocations in primary cutaneous marginal zone B-cell lymphoma

Haematologica 2004; 89(9):e113

Dear Sir,

Mucosa-associated lymphoid tissue (MALT) lymphomas include low-grade B-cell lymphomas from a number of extranodal sites, affecting both mucosal organs such as the salivary gland, lung, thyroid, conjunctiva, and liver and nonmucosal organs such as the orbit and the skin. These organs are devoid of any native lymphoid tissue, and the lymphoma arises from the MALT acquired as a result of a chronic inflammatory or autoimmune disorder.<sup>1</sup> Genetically, only 5% of MALT lymphomas show the t(1;14)(p22;q32), that causes BCL10 deregulation, which specifically links the antigen receptor signaling to the NFkB pathway.<sup>2</sup> The most frequent structural abnormality in MALT lymphomas is t(11;18)(q21;q21), that fuses the amino terminal of the API2 gene (11q21) to the carboxyl terminal of the MALT1 gene (18q21) and generates a chimeric fusion product that also activates NFkB.<sup>3</sup> This abnormality has been detected in 30%-50% of gastric MALT lymphomas, and also in other localizations (small intestine, large intestine, lung, conjunctiva, orbit and salivary gland) at marked variable frequencies.<sup>4</sup> Recently, Streubel et al reported a novel recurrent translocation t(14;18)(q32;q21) in MALT lymphoma involving IgH and MALT1 genes.<sup>5</sup> In primary cutaneous marginal zone B-cell lymphomas (PCMZL), there is a controversy regarding the existence of MALT1 translocations. Some authors have demonstrated the absence of t(11;18)(q21;q21) by polymerase chain reaction (PCR) methods and other MALT1 (18q21) rearrangements by fluorescence in situ hybridization (FISH) techniques<sup>4,6</sup> while others have shown the presence of MALT1 translocations such as t(14;18)(q32;q21)<sup>5</sup> in patients with PCMZL. The aim of the present study was to determine if PCMZL show MALT1 translocations.

Twenty-six samples from twenty-three patients affected with a PCMZL were included in the study. Sixteen were males and seven were females, with a mean age of 46 years. All cases were classified according to the EORTC and WHO classifications.<sup>1,7</sup> The diagnosis was established taking into account the clinical, cytological and immunophenotypical and molecular data. FISH was performed on paraffin sections from the affected skin areas using a MALT1 (18q21) dual color break apart translocation probe (VYSIS, Downers Grove, IL) to detect MALT1 translocations. One hundred nuclei were scored. In addition, ten peripheral blood samples from healthy donors were tested with the same FISH probe as controls. MALT1 translocations were not detected in any of the analyzed cases. In two paraffin sections from cases with PCMZL, some areas showed three copies of the MALT1 gene. However, in the control peripheral blood samples we detected until a 13% of the analyzed nuclei harbouring three copies of the MALT1 gene. Moreover, the finding of three copies of MALT1 gene in normal tissues was previously described by Krugmann *et al.*<sup>8</sup> when they analyzed their control samples (five normal gastric mucosa and ten cases of H pylori associated gastritis) and the cut of value for the detection of a partial trisomy 18 (of MALT1 gene) was set at 15% of nuclei with more than two signals of the probe.

The implication of MALT1 gene in the pathogenic pathway of PCMZL has been a matter of controversy. Streubel *et al.*<sup>5</sup> studied the presence of the recently

described t(14;18)(q32;q21) IgH/MALT1 in a large series of 66 MALT lymphomas of different localizations. Among them, 11 cases were PCMZL. Using a dual color interphase FISH assay, they found the implication of the IgH/MALT1 translocation in 3/11 cases (27%). Other authors have also analyzed the implication of MALT1 gene in the same pathology. Gronbaek *et al.*<sup>6</sup> examined the presence of t(11;18)(q21;q21) API2/MALT1 translocation in a series of 19 primary cutaneous B-cell lymphomas (PCBCL), being 12 of them PCMZL, by using RT-PCR technique and none of the cases showed any evidence of API2/MALT1 transcripts indicating that the t(11;18)(q21;q21) is not a typical feature of PCBCL. In addition, Ye *et al.*<sup>4</sup> studied the existence of API2/MALT1 translocation by RT-PCR and the presence of MALT1 translocations by FISH in 417 cases of MALT lymphomas, 27 of which were PCMZL and did not find MALT1 implication in any of these cases. In the present study, we have applied FISH technology with a MALT1 dual color break apart translocation probe that would detect all the possible translocations affecting MALT1 gene, including t(11;18)(q21;q21) API2/MALT1, t(14;18)(q32;q21) IgH/MALT1 and others. Our results agree with those found by Gronbaek *et al.*<sup>6</sup> and Ye *et al.*<sup>4</sup> and do not confirm the implication of MALT1 gene in PCMZL found by Streubel *et al.*<sup>5</sup> In conclusion, larger studies are warranted in order to determine the real incidence of MALT1 translocations in PCMZL.

Blanca Espinet,<sup>1,5,6</sup> Fernando Gallardo,<sup>2,6</sup> Ramon M<sup>a</sup> Pujol,<sup>2,6</sup>  
Teresa Estrach,<sup>3</sup> Octavio Servitje,<sup>4</sup> Francesc Solé<sup>1,5</sup>

<sup>1</sup>Laboratori de Citogenètica i Biologia Molecular. Servei de Patologia.  
Hospital del Mar. Barcelona, Spain;

<sup>2</sup>Servei de Dermatologia. Hospital del Mar. Barcelona, Spain;

<sup>3</sup>Servei de Dermatologia, Hospital Clínic, IDIBAPS, Universitat de  
Barcelona, Barcelona, Spain;

<sup>4</sup>Servei de Dermatologia, Hospital Universitari de Bellvitge, L'Hospitalet de  
Llobregat, Spain;

<sup>5</sup>Escola de Citologia Hematològica S. Woessner-IMAS. Hospital del Mar;  
IMAS. Barcelona, Spain

<sup>6</sup>URNHE-PRBB. Barcelona, Spain

*Acknowledgments:* This study was partially supported by the grants SAF-2001-4947, C03/07, C03/10 and G03/179 from the Instituto de Salud Carlos III, Spanish Ministries of Science and Technology and Health and Xarxa Temàtica de Limfomes Cutanis 2002/XT/02 from the Generalitat de Catalunya, Spain. The authors want to thank Carme Melero her excellent technical assistance.

*Key words:* Primary cutaneous marginal zone B-cell lymphomas (PCMZL), FISH, MALT1

*Correspondence:* Dra. Blanca Espinet

Laboratori de Citogenètica i Biologia Molecular. Servei de Patologia.

Hospital del Mar Passeig Marítim, 25-29 Barcelona 08003 Spain

Tel. 34-93-248.30.35 Fax. 34-93-248.31.31

E-mail: bespinet@imas.imim.es

## References

- Jaffe ES, Harris NL, Stein H, Vardiman JW (eds). World Health Organization classification of tumours. Tumours of hematopoietic and lymphoid tissues. IARC Press. Lyon, 2001.
- Willis TG, Jadayel DM, Du MQ, Peng H, Pery AR, Abdul-Rauf M, Price H, Karran L, Majekodunmi O, Wlodarska I, Pan L, Crook T, Hamoudi R, Isaacson PG, Dyer MJ. Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. *Cell* 1999; 96: 35-45.
- Dierlamm J, Baens M, Wlodarska I, Stefanova-Ouzounova M, Hernandez JM, Hossfeld DK, De Wolf-Peeters C, Hagemeijer A, Van den Berghe H, Marynen P. The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in

- the t(11;18)(q21;q21) associated with mucosa-associated lymphoid tissue lymphomas. *Blood* 1999; 93: 3601-9.
4. Ye H, Liu H, Attygalle A, Wotherspoon AC, Nicholson AG, Charlotte F, Leblond V, Speight P, Goodlad J, Lavergne-Slove A, Martin-Subero JJ, Siebert R, Dogan A, Isaacson PG, Du MQ. Variable frequencies of t(11;18)(q21;q21) in MALT lymphomas of different sites: significant association with CagA strains of *H pylori* in gastric MALT lymphoma. *Blood* 2003; 102: 1012-8.
  5. Streubel B, Lamprecht A, Dierlamm J, Cerroni L, Stolte M, Ott G, Raderer M, Chott A. T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. *Blood* 2003; 101: 2335-9.
  6. Gronbaek K, Ralfkiaer E, Kalla J, Skovgaard GL, Guldborg P. Infrequent somatic Fas mutations but no evidence of Bcl10 mutations or t(11;18) in primary cutaneous MALT-type lymphoma. *J Pathol* 2003; 201: 134-40.
  7. Willemze R, Kerl H, Sterry W, Berti E, Cerroni L, Chimenti S et al. EORTC classification for cutaneous lymphomas: a proposal from the cutaneous lymphoma study group of the European Organization for Research and Treatment of Cancer. *Blood* 1997; 90: 354-71.
  8. Krugmann J, Tzankov A, Dirnhofer S, Fend F, Greil R, Siebert R, Erdel M. Unfavourable prognosis of patients with trisomy 18q21 detected by fluorescence in situ hybridisation in t(11;18) negative, surgically resected, gastrointestinal B cell lymphomas. *J Clin Pathol* 2004; 57: 360-4.