Annals of Hematology (2019) 98:1513–1516
https://doi.org/10.1007/s00277-018-3565-5

LETTER TO THE EDITOR

Primary hepatic marginal B cell lymphoma of mucosa-associated lymphoid tissue (MALT) and non-alcoholic steatohepatitis (NASH): more than a coincidence?

Simon Haefliger[1] · Dina Milowich[1] · Amedeo Sciarra[1] · Mounir Trimeche[1] · Justine Bouilly[1] · Julie Kaiser[2] · Stephanie Volpi[3] · Jean-Philippe Brouland[1] · Christine Sempoux[1] · Laurence de Leval[1]

Received: 15 August 2018 / Accepted: 19 November 2018 / Published online: 28 November 2018

Dear Editor,

A 69-year-old man was referred to our institution for investigation of abnormal liver function tests (alanine transaminase, 87 IU/l ($N < 50$) and gamma-glutamyltranspeptidase, 233 IU/l ($N < 66$)). The patient, known for a metabolic syndrome with type 2 diabetes, hypercholesterolemia, hypertension, and BMI (kg/m^2) of 39.2, had no history of alcohol abuse. Viral (HBV, HCV, and EBV) and autoimmune serologies were negative and no intake of relevant medication was reported. An ultrasonography revealed a 2.1-cm hypoechoic liver mass, mildly T2-hyperintense on magnetic resonance imaging (MRI), with a partial washout on portal venous phase. A needle biopsy of the nodule showed extensive obliteration of the liver parenchyma by a dense lymphoid infiltrate, expanding the portal tracts and spilling on the lobules (Fig. 1a). The lymphoid cells were mostly small to medium-sized, with slightly irregular nuclei and moderately abundant pale cytoplasm, with a CD20+, CD5−, CD10−, CD23, CD43+/−, CyclinD1−, BCL2+, BCL6−, IRTA1−/+, IgM Kappa immunophenotype (Fig. 1b–e). Ki67 proliferation index was < 10%. Immunostains also evidenced colonized follicles sustained by CD21+ dendritic cells, comprising residual BCL6+ BCL2− germinal center B cells, and lympho-epithelial lesions amongst cytokeratin 7-positive bile ducts (Fig. 1f). Fluorescent in situ hybridization (FISH) examination did not demonstrate *MALT1* gene rearrangement. The uninvolved liver (Fig. 1g–h) was characterized by macrovesicular steatosis grade 2, foci of ballooned hepatocytes with few inflammatory cells, and marked perisinusoidal fibrosis together with mild portal fibrosis (steatosis-activity-fibrosis (SAF) score [1] of S2A3F2). These findings were diagnostic for hepatic marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and non-alcoholic steatohepatitis (NASH). Staging procedures including total body computed tomography and bone marrow biopsy showed no distant lesion. Gastroscopy showed no lymphomatous infiltration but revealed *Helicobacter pylori* (HP)–associated gastritis. The patient was treated with 4 cycles of rituximab and HP eradication therapy. Follow-up MRI at 6 months showed partial regression (30%) of the hepatic mass.

✉ Simon Haefliger
s.haefliger@hotmail.com

[1] Institute of Pathology, Lausanne University Hospital, Lausanne, Switzerland

[2] Department of Hematology, Lausanne University Hospital, Lausanne, Switzerland

[3] Department of Radiology, Lausanne University Hospital, Lausanne, Switzerland

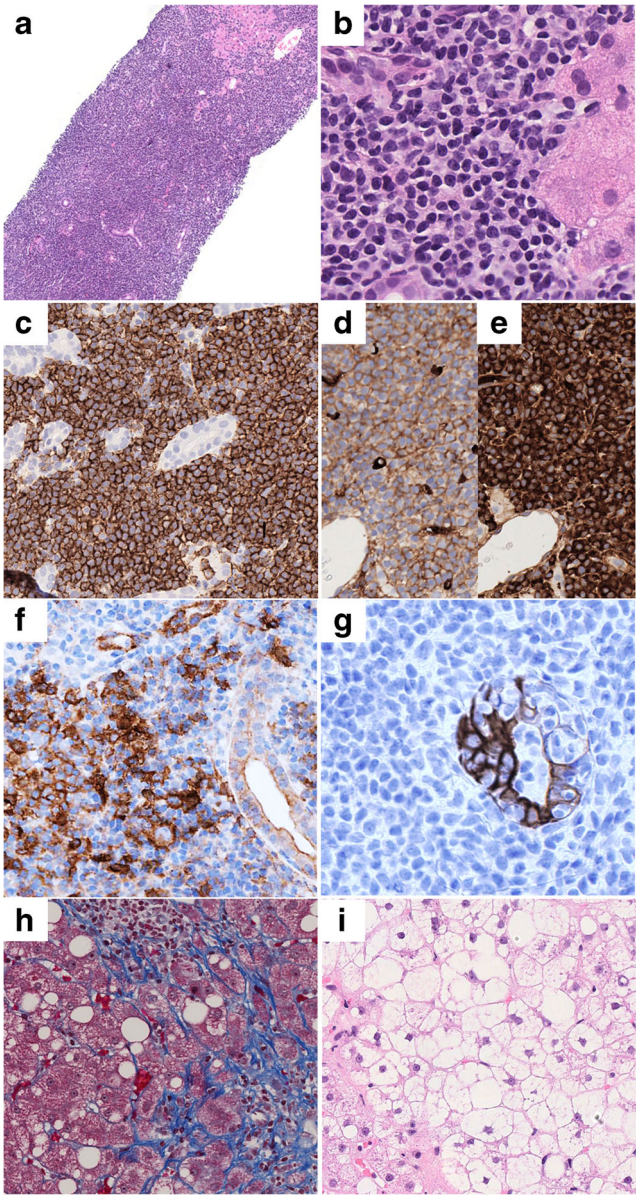

Fig. 1 **a** Low power view of hepatic biopsy. A dense lymphoid infiltrate expanded the portal tracts and extended into the lobules that were largely obliterated (hematoxylin and eosin (HE), × 4). **b** The lymphoid population was composed of small to medium-sized lymphocytes, with slightly irregular nuclei and moderately abundant pale cytoplasm (HE, × 40). The lymphoid cells were diffusely CD20-positive (**c**, immunoperoxidase, × 20), negative for lambda (**d**, immunoperoxidase, × 20), strongly positive for kappa light chains (**e**, immunoperoxidase, × 20), and focally positive for IRTA1 (**f**, immunoperoxidase, × 20). **g** CK7 highlights the bile ducts disrupted by prominent lympho-epithelial lesions (immunoperoxidase, × 40). Non-tumoral liver featured a marked perisinusoidal fibrosis (**h**, trichrome, × 20) and macrovesicular steatosis with ballooned hepatocytes (**i**, HE, × 20)

DNA extracted from the liver biopsy was analyzed by a custom panel of 54 genes relevant to mature B cell lymphoma biology using NGS technology. Interestingly, two likely pathogenic frameshift mutations were found in the *tumor necrosis factor alpha (TNF-alpha) inducible protein 3*, *TNFAIP3* gene (p.Val115Alafs*9) and in the *cyclic adenosine monophosphate (cAMP) response element binding protein*, *CREBBP* gene (p.Ile1084Asnfs*3) (Fig. 2). Mutations of these two genes have been described in MALT lymphomas, particularly in those of ocular origin [2, 3]. Mechanistically inactivating mutations or deletions of *TNFAIP3* will upregulate the NF-kB pathway, which is commonly activated in lymphomagenesis [4], whereas inactivation of *CREBBP* promotes lymphomagenesis through regulation of apoptosis and immune evasion [3].

Primary hepatic MALT lymphoma is a very rare, indolent lymphoma with slightly more than 70 cases reported in the literature [5–7]. In general, MALT lymphomas in other organs arise in the background of local chronic inflammation driven by bacterial infections (*H. pylori*, *Chlamydia psittaci*, or *Borrelia burgdorferi*) or by autoimmunity, like Hashimoto thyroiditis or Sjögren syndrome [8, 9]. Interestingly, a substantial number of primary hepatic MALT lymphomas were reported to occur in patients with chronic hepatitis B or C ($n = 26$), or with primary biliary cirrhosis ($n = 4$) [6, 10, 11] suggesting a link between chronic liver inflammation and hepatic MALT lymphomagenesis. Another potential link is with HP infection, since concomitant HP-associated gastritis was described in eight patients with hepatic MALT lymphoma [6], and HP-species have been detected in the bile of patients with and without hepatobiliary cancer [12]. Our case, the first primary hepatic MALT lymphoma analyzed on a mutational level, represents also the first reported association of primary hepatic MALT lymphoma with NASH, questioning whether NASH, besides its established role in hepatocellular carcinogenesis [13], could act as a possible inflammatory trigger of lymphomagenesis. In our case, it could be hypothesized that TNF-alpha, an important cytokine mediator in NASH and chronic inflammation [14], could represent a possible mechanistic link with lymphomagenesis by potentiating the activation of the NF-kB pathway [15]. Since metabolic syndrome and its complications [16] represent a worldwide growing concern, this question of NASH-promoting lymphomagenesis deserves further examination.

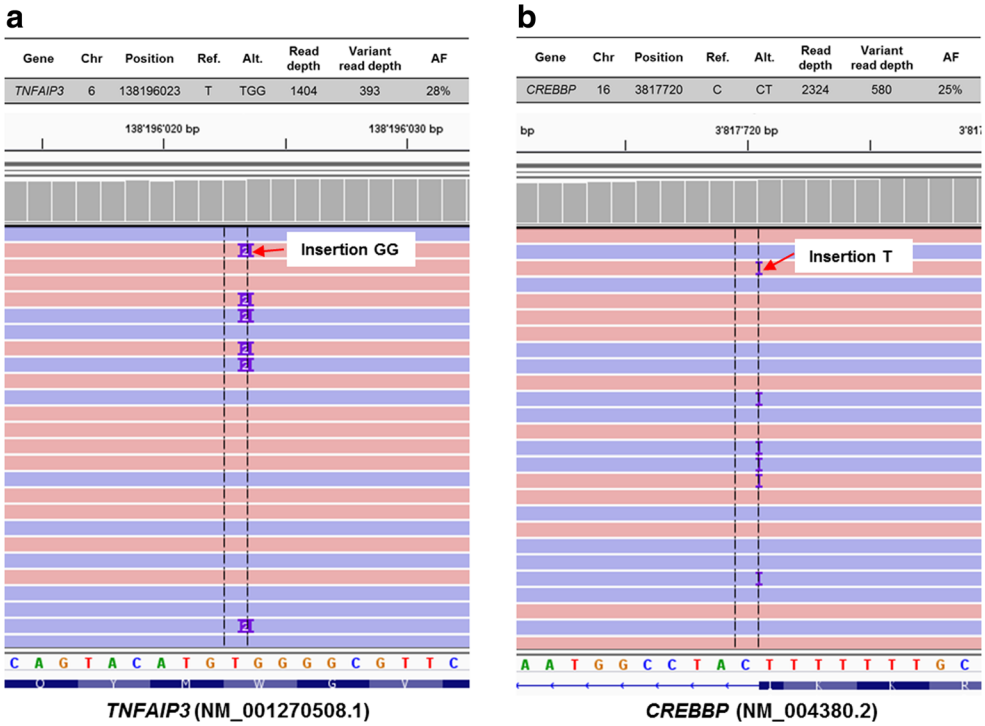

Fig. 2 Illustration of the *TNFAIP3* c.340_341dup (**a**) and the *CREBBP* c.3250dup (**b**) alterations found in affected tissue sample visualized with the Integrative Genomic Viewer (IGV) software, estimated proportion of tumor cells in the analyzed sample 60%. Forward and reverse reads are shown in red and blue, respectively, mean coverage, 2085X. DNA from formalin-fixed paraffin-embedded tumor sample was sequenced targeting a custom panel of 54 genes representing those most frequently mutated in B cell lymphomas (list available on request). Amplifiable genomic DNA was processed with IDT xGen® Hybridization with xGen Predesigned Gene Capture Pools (IDT) customized for use with KAPA Hyper Library prep. Capture-based and amplified targets were sequenced on a MiSeq instrument (Illumina) and analyzed with our in-house pipeline. AF, allele frequency; Ref., reference nucleotide; Alt., altered nucleotide

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from the patient.

References

1. Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, Tordjman J, Clement K (2012) Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Hepatology 56:1751–1759. https://doi.org/10.1002/hep.25889
2. Moody S, Thompson JS, Chuang SS, Liu H, Raderer M, Vassiliou G, Wlodarska I, Wu F, Cogliatti S, Robson A, Ashton-Key M, Bi Y, Goodlad J, du MQ (2018) Novel *GPR34* and *CCR6* mutation and distinct genetic profiles in MALT lymphomas of different sites. Haematologica 103:1329–1336. https://doi.org/10.3324/haematol.2018.191601
3. Jung H, Yoo H, Lee SH et al (2018) The mutational landscape of ocular marginal zone lymphoma identifies frequent alterations in *TNFAIP3* followed by mutations in *TBL1XR1* and *CREBBP*. Oncotarget 8:17038–17039. https://doi.org/10.18632/oncotarget.14928
4. Du MQ (2016) MALT lymphoma: a paradigm of NF-κB dysregulation. Semin Cancer Biol 39:49–60. https://doi.org/10.1016/j.semcancer.2016.07.003
5. Zucca E, Conconi A, Pedrinis E et al (2003) Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Blood 101:2489–2495. https://doi.org/10.1182/blood-2002-04-1279
6. Dong S, Chen L, Chen Y et al (2017) Primary hepatic extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type: a case report and literature review. Medicine (Baltimore) 96:e3605. https://doi.org/10.1097/MD.0000000000006305
7. Baumhoer D, Tzankov A, Dirnhofer S, Tornillo L, Terracciano LM (2008) Patterns of liver infiltration in lymphoproliferative disease. Histopathology 53:81–90. https://doi.org/10.1111/j.1365-2559.2008.03069.x
8. Thieblemont C, Bertoni F, Copie-Bergman C, Ferreri AJM, Ponzoni M (2014) Chronic inflammation and extra-nodal marginal-zone lymphomas of MALT-type. Semin Cancer Biol 24:33–42. https://doi.org/10.1016/j.semcancer.2013.11.005
9. Smedby K, Ponzoni M (2017) The aetiology of B-cell lymphoid malignancies with a focus on chronic inflammation and infections. J Intern Med 282:360–370. https://doi.org/10.1111/joim.12684
10. Bao C, Wei J, Zhao X, Lin L, Chen D, Liu K, Qian W, Anas JM, Zhao K (2018) Prognostic value of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography in primary hepatic mucosa-associated lymphoid tissue lymphoma: a case report and review of the literature. Medicine (Baltimore) 97:e9877. https://doi.org/10.1097/MD.0000000000009877

11. Gherlan GS, Stoia R, Enyedi M et al (2016) Primary hepatic marginal zone lymphoma in a patient with chronic hepatitis C. Mædica 11:250–254
12. Fukuda K, Kuroki T, Tajima Y et al (2002) Comparative analysis of helicobacter DNAs and biliary pathology in patient with and without hepatobiliary cancer. Carcinogenesis 23:1927–1931. https://doi.org/10.1093/carcin/23.11.1927
13. Cholankeril G, Patel R, Khurana S, Satapathy SK (2017) Hepatocellular carcinoma in non-alcoholic steatohepatitis: current knowledge and implications for management. World J Hepatol 9: 533–543. https://doi.org/10.4254/wjh.v9.i11.533
14. Braunersreuther V, Viviani GL, Mach F et al (2012) Role of cytokines and chemokines in non-alcoholic fatty liver disease. World J Gastroenterol 18:727–735. https://doi.org/10.3748/wjg.v18.i8.727
15. Taniguchi K, Karin M (2018) NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol 18:309–324. https://doi.org/10.1038/nri.2017.142
16. Huang Y, Cai X, Mai W et al (2016) Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ 355:i5953. https://doi.org/10.1136/bmj.i5953