Mediterranean Journal of Hematology and Infectious Diseases

Review Article

Infections and Follicular Lymphoma: is there a Link?

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Competing interests: The authors have declared that no competing interests exist.

Abstract. Several infectious agents appear to provide a proliferative signal -- "antigen-drive" – that could be implicated in the pathogenesis of various type of Non-Hodgkin Lymphoma (NHL). A classical model of the infection-driven lymphoproliferative disorder is Helicobacter pylori-induced gastric MALT lymphoma, where antibiotic therapy allows the eradication of both the infectious agent and the clonal B-cell expansion. Following the footsteps of this example, several retrospective studies have found a correlation with other pathogens and B-cell Lymphomas, adding new relevant information about pathogenesis and laying the groundwork for chemotherapy-free treatments.

Although no clear association has been found between infectious agents and Follicular Lymphoma (FL), a growing number of biological and clinical observations suggests the interaction of physiological and pathological microbial populations also in this subtype of lymphoma. In the last few years, epidemiological studies investigating the association of known risk factors and FL found a potential correlation with viral or bacterial infections; moreover, recent findings of the stimulation of FL clones support the importance of microbial exposure to lymphomagenesis and disease progression.

In the following review we make an attempt to find tangible evidence for a role of either physiological and pathological exogenous microbial species in the pathogenesis of FL, and try to integrate the findings coming from epidemiological, biological and interventional studies to define future novel treatment and prevention strategies for FL.

Keywords: Follicular Lymphoma, Bacterial Infections, Viral Infections.

Citation: Zallio F., Limberti G., Ladetto M. Infections and Follicular lymphoma: is there a link? Mediterr J Hematol Infect Dis 2017, 9(1): e2017035, DOI: http://dx.doi.org/10.4084/MJHID.2017.035

Published: May 1, 2017 **Received: November 8, 2016** **Accepted: March 17, 2017**

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Introduction. FL is the second most common form of NHL, accounting for approximately 30% of NHL cases. The disease is characterized by a slow progression and high response rates to therapy, that is the reason why it is considered the prototype of indolent lymphomas; median survival is currently around 14 years, with most patients displaying an indolent form of the disease, slowly progressing over many years. Nonetheless, most patients eventually develop increasingly resistant disease over time, and in up to 45% of cases, the original indolent subtype transforms into an aggressive subtype, an event that is associated with a poor outcome.[1,2,3]

The first hit of the oncogenic cascade leading to FL is attributed to the t(14;18) chromosomal translocation that occurs in an early B cell stage in the bone marrow. Naive B cells, carrying the t(14;18), exit the bone marrow and colonize secondary lymphoid tissue, where they undergo

the germinal center reaction but have a survival advantage due to their constitutive expression of BCL2, which is not normally expressed in the germinal center.[4]

Apart from the t(14;18), recurrent secondary genetic alterations including genomic gains, losses, and mutations (i.e. alterations in MLL2, EPHA7, TNFRSF14, and EZH2) could provide a growth advantage to the neoplastic cells. Moreover, the crosstalk between neoplastic B cells and the microenvironment plays an important role in sustaining tumor cell growth and eventually promoting transformation.[5] Current treatment strategies vary from the classical watch and wait approach to the use of anti CD20 monoclonal antibodies (labeled or unlabeled with radioimmunoconjugates) in combination with chemotherapy, while more aggressive treatment approaches including autologous or allogeneic stem cell transplantation are reserved to patients with more resistant disease.[6]

Recently a large bulk of molecular and clinical research has been performed to better understand the molecular mechanisms of lymphomagenesis and to develop non-chemotherapeutic agents active in specific lymphoma subtypes; in this field infectious agents could represent therapeutic targets for lymphoma treatment toward chemotherapy-free therapeutic approaches.

Despite huge advances in the comprehension of the genetic anatomy of FL, the potential epidemiologic role of environmental stimuli has not been clearly established; this is somehow in contrast to the huge bulk of knowledge which has been accumulated in MALT lymphomas. Nevertheless, a number of biological and clinical observations suggests that interaction with physiological and pathological microbial populations might play a role also in FL.

A classical model of the infection-driven lymphoproliferative disorder is *Helicobacter pylori*-induced gastric MALT lymphoma where antibiotic therapy allows eradication of both the infectious agent and the clonal B-cell expansion, leading to long-term complete remissions (CR).[7]

The identification of this pathogen as the causative agent in gastric MALT lymphomas have resulted in substantial progress in understanding the physiopathology of the disease permitting to develop new therapeutic strategies. The list of lymphomas evolving in response to antigen (bacterial or viral) has been growing rapidly in recent years, associated in some cases with similar therapeutic success.[8] Although no such association with infectious agents or other early specific therapeutic target has yet been identified for FL, this concept seems ideally suited to such an indolent disease.

This review summarizes current evidence for a role of either physiological and pathological exogenous microbial species in the pathogenesis of FL. So, we underwent an extensive literature search focusing on clinical observations suggesting such correlations, and we tried to underline potential similarities between FL and other indolent lymphoproliferative processes where the role of microbial organisms is clearly established.

Role of Infection in other Lymphomas. In recent years, a growing number of exogenous microbial agents have been linked to NHL. The *Helicobacter pylori* (HP), *Chlamydia psittaci* and hepatitis C virus are best-known examples, but other agents have been identified in the pathogenesis of more rare subtypes of NHL; these associations are important because they have clinical and therapeutic implications and provide novel insights into the mechanisms that govern lymphoma development.[9]

HP is a Proteobacteria Epsilon bacterium known to cause stomach ulcers and chronic gastritis. Its role in the pathogenesis of the majority of cases of gastric MALT lymphoma was demonstrated nearly twenty years ago.

HP affects about 50% of the world's population even if only 1–2% of infected individuals will develop a malignant disease. The pathogenetic role of HP is related to the oncogenic properties of the cytotoxin-associated antigen A (Cag-A), a protein that is able to activate the signaling pathway leading to the activation and upregulation of the antiapoptotic molecule BCL2.[10,11] Three major chromosomal translocations specific of MALT lymphomas are reported, i.e. t(11;18) which is the most common (found in nearly 30% of the cases), t(14;18) and t(1;14). HP eradication using a combination of antibiotics and proton-pump inhibitors (PPI), represents the standard treatment of HP-associated MALT-lymphomas, leading to lymphoma regression in about 75% of patients.[12]

Chlamydophila psittaci belongs to the family of Chlamydiae and is the second most studied among

bacteria having a pathogenetic role in MALT-lymphomas. *Chlamydophila psittaci* can cause a lung infection called psittacosis. DNA from this bacterium has been found in biopsies of MALT lymphoma of the ocular adnexa. The finding that *C. psittaci* infection has been detected in up to approximately 80% of Italian patients with ocular adnexa MALT lymphoma provided the rationale for the antibiotic treatment of localized lesions. Moreover, the eradication of *C. psittaci* infection with doxycycline for patients with ocular adnexa MALT lymphoma resulted in lymphoma regression in approximately 50% of patients.[9]

Epstein-Barr virus (EBV) is the first Human Herpes Virus found to be associated with the pathogenesis of cancer. EBV has a worldwide distribution, being able to establish a lifelong infection in more than 90% of individuals. Primary infection is usually asymptomatic or could cause a benign lymphoproliferative disease, known as infectious mononucleosis.

EBV has a successful strategy to reside in the hematopoietic system, including the establishment of a nonpathogenic latent infection of memory B lymphocytes that allows the virus to persist for the lifetime. According to current knowledge, latent antigens encoded by EBV interfere with a number of critical cellular pathways, thereby promoting oncogenesis. Although human EBV infection may lead to the development of a variety of hematopoietic and epithelial cancers, most common cases result from the transformation of infected B cells into lymphoproliferative disorders:[13] Hodgkin lymphomas, diffuse large cell and Burkitt lymphomas. Moreover, EBV can cause a rare but potentially fatal complication in hematopoietic stem cell transplants, as well as in solid-organ recipients, known as EBV-associated post-transplant lymphoproliferative disease (PTLD).[14,l5,16]

Human Immunodeficiency Virus (HIV) is a lentivirus of the retroviridae family that integrates itself into host chromosomal DNA. The increased risk for lymphoma appears related to multiple factors, including the transforming properties of the virus itself, the immunosuppression and, most importantly, opportunistic infections associated with other lymphotropic herpes viruses such as EBV and human herpesvirus 8. Aggressive lymphomas account for the vast majority of cases. The clinical outcome appears to be worse than in similar aggressive lymphomas in the general population. However, following the introduction of highly active antiretroviral therapy, the risk of developing lymphoma in the context of HIV infection has decreased, and the clinical outcome has improved.[17]

Hepatitis C virus (HCV) is a small RNA virus of the Flaviviridae family; is a hepatotropic and lymphotropic virus responsible for acute hepatitis and chronic liver disease; the presence of HCV is associated with a spectrum of lymphoproliferative disorders, ranging from polyclonal B-cell expansion to overt malignant lymphoma. Indeed, as well as small B-cell clones can be detected in bone marrow or liver biopsies, a higher frequency of lymphoid malignancies has been reported in HCV-positive patients. The association between HCV infection and NHL has been demonstrated by epidemiological studies, in particular in highly endemic geographical areas such as Italy, Japan, and southern parts of United States. In these countries, together with diffuse large B-cell lymphomas, marginal zone lymphomas are the histotypes most frequently associated with HCV infection. The most convincing argument for a causative link between HCV and lymphoproliferation is represented by studies demonstrating the eradication of the neoplastic clone by the antiviral treatment in HCV-positive patients affected by indolent NHL (18). Analogous to what has been observed in HP-associated gastric, the role of HCV infection in lymphomagenesis may be related to the chronic antigenic stimulation of B-cell immunologic response by the virus.[19,20]

Adult T-cell leukemia-lymphoma (ATL) is an aggressive lymphoid proliferation associated with the human lymphotropic virus type I (HTLV-I). ATL usually occurs in people from HTLV-I endemic regions, such as southern Japan and the Caribbean. HTLV-I causes transformation and clonal expansion of T cells, resulting in ATL in approximately 1%-5% of the infected hosts, with a mean latency period of > 50 years. ATL carries a bad prognosis because of intrinsic chemoresistance and severe immunosuppression. Recently, a worldwide meta-analysis revealed that the combination of zidovudine and IFN-α is highly effective in the leukemic subtypes of ATL and should be considered as standard first-line therapy in this setting.[21]

Human herpesvirus 8 (HHV8) is a gammaherpesvirus associated with primary

effusion lymphoma, a lymphoproliferative disease that is rarely observed in immunocompromised individuals. These neoplastic disorders that result from HHV8 infection are most commonly related to immunodeficiency states, including HIV infection and EBV infection. The lymphoma is characterized by the localization in one of the body cavities (pleural, pericardial, or peritoneal cavity), without lymph node enlargement and lymphadenopathy. Prognosis is very poor, with a median survival of 6 months.[22]

Epidemiological Evidence. Given the heterogeneous nature of lymphoma subtypes and their different clinical behavior, it is intriguing to identify the risk factors potentially responsible for the occurrence of NHL, so various occupational, environmental and chemical agents have been claimed by several epidemiological studies. However, although for some factors the correlation seems to exist, definite conclusions have not been drawn. Several reports have also investigated the possible association between infection-related conditions and the occurrence of NHL; in fact, several infectious agents have been identified as causative factors for the development of NHL, most likely due to their induction of DNA damage, inflammatory cells proliferation, and cytokine release.

To address this issue the International Lymphoma Epidemiology Consortium (InterLymph), an open scientific forum for epidemiological research funded in 2001, undertook the NHL Subtypes Project; this is an international group of multidisciplinary specialists, who have worked together with the aim of identifying associations of several risk factors across different lymphoma subtypes.[23]

Regarding FL, in 2013 a large pooled analysis carried on by the Interlymph Consortium made an attempt to assess associations between medical, hormonal, family history, lifestyle and occupational factors with the risk of developing FL. The incidence rate of FL was reported as higher in western countries, which comprises ~30% of NHL, with a white to black ratio of 2:3, and relatively rare in developing and Far Eastern countries. Moreover, FL risk was increased in subjects with a first-degree relative with non-Hodgkin lymphoma in spray painters among women with Sjögren and among cigarette smokers and obese subjects. No specific observation mentioned a link between infection and risk of FL.[24]

Another large retrospective case–control study using SEER and Medicare database investigated the role of infection-related conditions and different NHL subtypes.[25] Cases were defined as individuals with a SEER diagnosis of primary lymphoid malignancy between 1992 and 2005. The database identified respiratory and skin infections to be associated with an increased risk of NHL in individuals aged more than 66 years. Claims for sinusitis, laryngitis and herpes zoster were present in the history of FL patients, sinusitis, laryngitis and herpes zoster were significant at longer latencies. Most FL cases carried the t(14;18), which was hypothesized to be transformed by exogenous antigen stimulation, such as from a viral infection.[26] Antigenic stimulation and/or subclinical immune deficiency, predisposing patients to both infections and lymphoma, were claimed as possible association between infection-related conditions and lymphoma.

Biological Evidence. The gene sequence for the immunoglobulin (Ig) heavy-chain (H) and light-chain (L) variable regions are assembled in the early stages of B-cell development in the bone marrow from distinct variable (V), diversity (D) and joining (J) segments through a process of somatic DNA rearrangement known as V(D)J recombination. In later stages, which takes place in the germinal center (GC) of the secondary lymphoid tissues, naive B-cells with low-affinity functional surface Ig (sIg) are induced to proliferate. The high proliferation rate is associated with somatic hypermutation of Ig genes, a process that introduces a high incidence of mutations within the V region of genes. Somatic hypermutation is thought to be a prerequisite for affinity maturation of antibody response. At this stage, normal B cells that are specific for an antigen are induced to operate a selection process that expands the population of B cells with an optimal binding affinity for the antigen.

Also, B cells carrying the t(14;18) exit the bone marrow and colonize the GC of secondary lymphoid tissue; subsequently they undergo somatic hypermutations of IgVH-genes, with mutational patterns very similar to their normal

counterpart, but with a survival advantage due to the constitutive expression of BCL2.

Recent studies by Schneider et al. demonstrated that somatic hypermutations occurring in FL cells could introduce sugar moieties, like high-mannose-terminated glycan, into the variable domain of the surface Ig antigen-binding sites, which create potential novel binding sites to mannose-specific lectins. In FL cells, B-cell receptor (BCR) expression is retained, despite the characteristic chromosomal translocation t(14;18), because BCR is fundamental for the transduction of the signals that maintain the survival and growth of FL clones. BCR variable-region mannoses in FL are recognized by lectins of common opportunistic bacteria, such as *Burkholderia cenocepacia* and *Pseudomonas aeruginosa*, that are usually found in soil and water; these lectins represent a potent stimulus for the proliferation of B cells expressing this kind of glycan-terminated glycan.[27,28,29] Therefore, these studies directly support the potential importance of microbial exposure in the proliferation and survival of FL clones, and they might be a key to a better understanding of the pathogenesis of FL.

Clinical Evidence. Although an expanding literature has examined several risk factors potentially correlated with the occurrence of FL, the etiology of the proliferative stimulus is generally unknown, and the few relationships observed suggest a complex multifactorial etiology.

A recent meta-analysis, selecting more than 20 articles, showed a more than two-times increase in the odds of developing NHL in patients with HBV infection. Interestingly, regarding FL subtype, a trend toward statistical risk was observed in countries with a high prevalence of HBV infection while no statistical risk was seen in countries with a low prevalence of HBV infection.[30]

The conclusion of the study was that was difficult to determine if the increased risk of FL in areas of high prevalence of HBV infections is due simply to a larger number of HBV infections or a true causal relationship. In the latter case, HBV might be responsible for lymphomagenesis through a chronic stimulation of B-cells which may predispose to DNA damage and transformation into neoplastic cells, or through an immunologic response to chronic local antigenic stimulation.

As opposed to HBV, a case-control study carried on by the InterLymph did not show an increased association between HCV infection and FL, that was restricted to other specific B-NHL subtypes like diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma, and lymphoplasmacytic lymphoma.[19]

An interesting clinicopathological finding came up from a Spanish study that analyzed a retrospective series of 58 patients with a diagnosis of HCV-positive B-cell lymphoproliferative disorder; eight of them were affected by FL, and at least half of them expressed BCL2 and p53.

Interestingly, the authors reported a cohort of 11 patients in which a clonal B cell expansion in the peripheral blood and bone marrow could be revealed, in the absence of conclusive histological evidence of neoplastic infiltration. These expanded clones make up a definite group of HCV-associated monoclonal B-cell Lymphocytosis that should be monitored because a 10% risk of evolution to overt lymphoma has been demonstrated.[31]

Currently, the association between EBV and follicular lymphoma is reported only in the form of isolated case reports in patients with various form of immunodeficiency or in the context of transformation to diffuse large cell lymphoma or classical Hodgkin lymphoma. Mackrides et al. analyzed 382 cases of FL consecutively diagnosed at the University of Miami and Stanford, in order to provide an estimated prevalence of EBV-positive FL; all the cases were tested for the expression of EBV-encoded small RNA (EBER) as determined by in situ hybridization. They identified 10 cases of EBV-positive FL (prevalence=2.6%) with a significant prevalence of grades 3A-3B FL (9 out of 10) and frequent strong coexpression of CD30; all cases demonstrated progression of the disease to a higher grade FL or diffuse large B-cell lymphoma. Given the increased incidence of EBV in high-grade FL and the fact that the cases are clinically and morphologically indistinguishable from EBV-negative FL patients, the authors suggested the screening for EBER in all high-grade cases.[32]

Recently an intriguing association between *Coxiella burnetii*/Q fever and the incidence of B-cell lymphomas was proposed by Melenotte et al. in a large scale study.[33] Starting from the observation of the occurrence of lymphoma in a patient with Q fever, they screened over 1000

consecutive patients of the French National Referral Center for Q fever database and examined if there was an association between the two diseases. An excess risk of DLBCL and FL was found in individuals who had Q fever compared with the general population and above all patients with a persistent localized infection were found to have a greater risk of lymphoma. These results support the evidence that a novel factor should be added to the list of bacteria that promote human B-cell lymphomas, in particular, FL.

The most relevant studies reporting a link between Follicular lymphoma and infectious agents are summarized in **Table 1**.

Taken in mind the gastric MALT as a well-accepted example of antigen-driven neoplastic cell proliferation, Portlock et al. explored the association between infectious agents and NHL in a cohort of 56 patients with an untreated advanced non-bulky indolent lymphoma.[34] All patients were tested for HP, HCV, *Borrelia burgdorferi*, *Chlamydia psittaci* and small bowel bacterial overgrowth; in this series, a documented infection was found in 37% of the patients, with a prevalence of HP. Starting from the observation of anecdotal lymphoma remissions after antibiotic therapy in a series of patients not requiring chemotherapy, they speculated that a prevention strategy would decrease the risk of future lymphoma progression driven by such antigens. Therefore in 2007, they launched a prospective clinical trial testing the role of prolonged clarithromycin antibiotic therapy as a first treatment in the same category of indolent advanced-stage lymphoma patients. Although the small sample size, they reported lymphoma objective responses in 9 of 32 patients (28.1%) with a long treatment-free survival for patients responding to antibiotics.[35]

The association between infectious agents and FL added new important information about the role played by the antigen stimulation in FL; moreover, the possibility to treat the neoplastic disease in a simple and efficient way could be considered a step toward developing a lymphoma preventive strategy by reducing the "antigen drive."

Discussion. In the last years, several infectious agents, like Hepatitis C, Human Immunodeficiency, and Epstein-Barr viruses, and *Helicobacter Pylori*, *Chlamydia psittaci,* and *Coxiella Burnetii* bacteria have been reported as involved in the malignant transformation of B or T lymphocytes, and therefore associated with the pathogenesis of lymphoproliferative disorders. While this hypothesis has been demonstrated for some rare subtypes of NHL, for the majority the evidence is uncertain. Regarding FL, based on available data, evidence linking this lymphoma subtype and exogenous infectious agents are weak, and currently, FL cannot be considered as an infection-driven disease. However, some clinical, epidemiologic studies and case reports indicate that it is still somehow premature to conclude that exogenous agents have a negligible role in the genesis of FL.

It has been estimated that chronic infections caused by viruses, bacteria, and parasites are the causative agents of nearly 10-15% of global cancers burden.[36,37] These infectious agents promote a cascade of events culminating in chronic inflammatory responses. Chronic antigenic stimulation has been postulated as a potential mechanism for carcinogenesis, thus predisposing target tissues to increased cancer susceptibility. In particular, in antigen-driven hematologic malignancies, like HP-associated with MALT, the chronic stimulation of the innate immune system causes a clonal expansion of B-lymphocytes, which leads to the production of oxidative reactions; these events result in genetic alterations, which eventually result in the development of a neoplastic monoclonal lymphoproliferation. As well as for MALT lymphomas, also for FL could be postulated an

Table 1. Links reported in the literature between Follicular Lymphoma and infectious agents.

Type of infectious agent (virus or bacteria)	***Number of patients included in the study***	***Prevalence of FL cases related to the infectious agent***	***P=***	***Source***
Hepatitis B virus	1377	Not mentioned	Odds ratio:1.66	Ref.30
Hepatitis C virus	1181	23	0.10	Ref.19
Hepatitis C virus	58	8	Not mentioned	Ref.31
Epstein-Barr virus	382	10	Not mentioned	Ref.32
Coxiella Burnetii	1468 cases of Q fever	1	NS	Ref. 33

inflammatory response secondary to an infectious-driven chronic antigenic stimulation, inducing t(14:18) translocation, leading to the transformation of a germinal center-derived B-cell. Apart from HP and other few microorganisms that colonize the gastrointestinal tract, it should be kept in mind that little is known about the complex community of human microbiota which includes more than 10^9 procaryotic cells per individual. Modern next generation sequencing tools for microbiome analysis are becoming widely available and intriguing correlations between the type of bacterial colonization in multiple districts, and some diseases have been established. Of note, human microbiota has some well-established differences among different world areas as also observed in several indolent lymphoid disorders. It is, therefore, advisable to further investigate this potential link by performing careful case-control or population analyses aiming at verifying whether specific pathological or nearly physiological microbiota patterns might be responsible for a chronic antigen stimulation in those lymphomas where a clearly responsible microorganism has still not been identified. Intestinal microbiota either directly or indirectly through the immune system can lead to aberrant DNA replication, particularly in some B lymphocytes which are vulnerable to genetic instability and activation, eventually affecting several pathways associated with lymphomagenesis.[38]

Finally, a chronic antigenic infectious stimulation was shown to be fundamental also in the cell perturbation of the microenvironment in sustaining the neoplastic cell growth. Indeed, also this pathway could play a role in the oncogenic cascade leading to FL,[39,40] and the encouraging results obtained by a novel panel of inhibitors of the signal transduction of the BCR, has led to further investigate the crosstalk between the downstream BCR signaling cascade and the microenvironment. The Btk inhibitor ibrutinib and the PI3Kδ inhibitor idelalisib have demonstrated good safety profile and promising clinical efficacy, affecting the survival of neoplastic B cells by preventing lymphocyte adhesion and homing, and inhibiting the microenvironment signals that commonly sustain the malignant clone.[41,42]

Conclusions. The pathogenesis of FL is a multistep process in which the t(14;18) translocation in a B lymphocyte appears to be fundamental for the initiation of the neoplastic cascade. Even if still unclear, infectious agents could play a role as a first hit responsible for the B-cell malignant transformation and growth. Precise elucidation of the mechanisms underlying lympho-proliferations may provide important clues for understanding how immune disturbance contributes to the development of this subtype of lymphoma. Moreover, the responses shown by BCR inhibitors and by antibacterial treatments, which can have cytoprotection properties like Rifaximin, considered a gut microenvironment modulator, provide an intriguing argument for a causative link between infectious agents and B-cell lymphoproliferation.

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