Antigen- and/or immune-driven lymphoproliferative disorders

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Introduction

Several lymphoproliferative disorders (LPDs) are believed to be instigated by transformation of a polyclonal population of normal lymphocytes to monoclonal neoplastic disorders in response to antigenic and/or immunological perpetrators [1–3]. The list of antigenic and immunological factors, as well as the corresponding lymphoma entities, is growing steadily [4–10]. In most of the antigen- and/or immune-driven lymphoproliferative disorders (AID-LPD), while the progression is a multistep process, the point at which a non-neoplastic lesion becomes neoplastic is not always precisely defined. Some of these lesions have a clonal abnormality that remains responsive to normal regulators of growth and differentiation, where the point of ‘clonal no return’ will be hard to define. The proliferations of the clones might be subclinical until additional genetic changes occur, where the process frequently becomes irreversible [11, 12]. The hypothesis of a multistep process is further established by the observation of a number of lymphoid lesions at the same time, each at a different stage of clonal evolution. Furthermore, multiclonal disease with different clones and occasionally dissimilar lymphoma types has been observed in patients with a profound immunosuppression, such as AIDS patients and those who receive intense immunosuppression following organ transplantation [13, 14].

The number of cell divisions, or the quantitative effect of polyclonal proliferation, increases the statistical probability of random chromosomal rearrangements that may deregulate an oncogene leading to an irreversible malignant process [15]. In immunocompetent individuals, the process of AID-LPD clonal evolution takes many years to develop; however, in profoundly immunocompromised patients, this process usually takes <1 year.

Although pathological features, as well as management approach, have been standardized for many of the AID-LPD, in many other entities it is difficult to standardize pathological features. In the latter entities, disease behavior can be variable, and not infrequently has poor correlation with pathology: a histologically aggressive appearing lesion may be a clinically indolent disease, and an apparently benign lesion may clinically behave very aggressively. When considering management of patients with AID-LPD, it is always pivotal to treat the underlying antigen or immunological factor and to improve immune status in immunosuppressed individuals.

In this review, we first intended to examine AID-LPD based on evidence deduced from animal models [1, 16–18]. We then analyzed the association between various AID-LPD and individual antigenic or immunological factors.

Animal models

Animal models of AID-LPD have been described in the literature, one typical example of which is East Coast Fever; an acute leukemia-like illness of cattle and Cape buffalo that is endemic in eastern, central and southern Africa, where the disease causes high mortality and losses in livestock production [16].

The disease is caused by the protozoan parasite Theileria parva. A peculiar feature of this infection is that the parasite survives only in a subset of T lymphocytes, leading to fatal T-cell LPD, associated with overexpression of casein kinase II gene with overproduction of casein kinase II, a serine-threonine-specific protein kinase, which serves as an oncogene, leading to lymphocyte transformation. Timely treatment of infected animals with antiparasitic drugs can cure this disease [17].

Another example of AID-LPD in animals is avian leukosis virus-associated lymphomas, where the neoplastic transformation results from activation of cellular c-myc gene by the virus; the pathological process involves the integration of the provirus upstream to the c-myc gene and transcription activation of this gene secondary to the insertion of strong viral promoter. The resultant RNA transcripts contain both viral and c-myc information, and are present at levels 30–100-fold higher than that of c-myc RNA in normal tissues leading to neoplastic transformation [1].

The third animal model example is Aleutin disease in mink, which is caused by a persistent parvovirus infection of the animal faced with a maximum but ineffective host immune response. The enormous immune response to the persistent infection in Aleutin disease ultimately causes systemic plasmacytosis and immune complex lesions, which eventually lead to the animal’s death [18]. A summary of these animal models is given in Table 1.
AID-LPD: proposed classification

We conducted a Medline search in which we reviewed all relevant articles from 1966 to the present, and we found AID-LPD to be a very heterogeneous group. The following is an attempt to classify these disorders, taking into consideration the antigen and/or immunological perpetrators, and the clinicopathological entities (Table 2; Figure 1).

I. Infection-related

A. Epstein-Barr virus-associated LPD

Epstein-Barr virus (EBV) is a human gamma herpesvirus with cell growth transforming ability that efficiently colonizes the B lymphoid system. Nine viral proteins contribute to transformation in vitro and at least five are believed to be essential for the transformation process [19]: the nuclear antigens EBNA-1 (the viral genome maintenance protein), EBNA-2, EBNA-3A and EBNA-3C, and latent membrane protein 1 (LMP1). The pathological mechanism of cell growth induction by these proteins is a subject of intense interest. Most progress in this area has been made with LMP1. LMP1 of EBV-infected cells plays an important role in this process by mimicking signals from the cell membrane to the nucleus through cytoplasmic tumor necrosis factor-receptor associated factors (TRAFs) [19]. In vivo, the pattern of EBV gene expression varies with different types of malignancies. The growth transforming infection is normally controlled by cytotoxic T lymphocyte (CTL) surveillance directed against virus latent cycle antigens. The persistence of the virus depends upon the establishment of a pool of non-cycling memory B cells that carry the virus genome but express only a limited number of viral antigens [20, 21].

The virus carrier state is usually asymptomatic. However, in rare occasions it can give rise to three distinct types of EBV-positive B-cell lymphoid disorders, each with a different in vivo pattern of viral latency as follows.

Burkitt’s lymphoma: a tumor of germinal center origin usually associated with type I latency, where the virus antigen expression is restricted to EBNA-1 and where defects in antigen processing function allow efficient tumor cell escape from CTL detection.

Hodgkin’s disease (HD): a post-germinal center lymphoid disorder usually associated with type II latency, where there is expression of latent membrane proteins LMP1 and -2 (in addition to EBNA-1).

Immunosuppression- and post-transplantation-associated LPD is usually associated with type III latency pattern. These lymphomas, at least in the initial stages, are directly EBV-driven and express the full spectrum of latent proteins, and remain susceptible to restoration of CTL surveillance.

Additionally, as will be discussed below, a rare association of EBV with T-cell lymphomas has been described.

i. Immunodeficiency-related, EBV-associated LPD.

a. Post-transplant lymphoproliferative disease (organ transplant related). Immunosuppressed organ transplant recipients are prone to the development of a clinically heterogeneous group of EBV-associated lymphoid prolifera tions referred to as post-transplantation lymphoproliferative disorder (PTLD). PTLDs were originally believed to be non-Hodgkin’s lymphoma (NHL), but their malignant status has been questioned because they frequently regress after reduction of immunosuppressive therapy [22]. PTLDs are most frequently EBV-driven B-cell proliferations, which can be polyclonal, oligoclonal, monoclonal or multicl onal, based on the phenotype or genotype [2, 23–28]. PTLDs are morphologically heterogeneous and their disease behavior is difficult to predict; in addition, they do not resemble any recognized entity that falls under lymphoid hyperplasia or lymphoid classification schemas, mainly due to the frequent polymorphic appearance of lymphoid cells in these lesions [23, 26]. In the allogeneic bone marrow transplantation setting, PTLD is most frequently seen in patients who have received intense immunosuppression in mismatched or matched unrelated transplant settings and recipients of T-cell depleted allografts [29, 30]. It is believed that the latently infected donor B cells may be a significant source of infection, but there are cases of lymphomas in B cells from seronegative donors, indicating that the virus is already present in the recipient and may cause proliferation of donor B cells [30, 31]. It is also possible that EBV may come from an exogenous third-party source (e.g. blood transfusion). Removal of donor B cells has been shown in some studies to decrease the risk of PTLD in T-cell-depleted bone marrow transplantation, and is thought to be secondary to reduced viral load or the virus target until the time that T cells begin to generate [32]. Recent studies have indicated that measuring EBV viral load in the peripheral blood by PCR can be useful in identifying organ transplant recipients at risk for development of PTLD, thereby providing the opportunity to alter immunosuppression when the tumors are most susceptible to immune modulation [33]. Limited treatment success has been reported after discontinuation of immunosuppressive therapy, administration of antiviral therapy, interferons and monoclonal antibodies [34, 35]. Recently, adaptive immunotherapy with unprimed peripheral mononuclear

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### Table 1. Animal models: summary of some known animal models of antigen- and/or immune-driven lymphoproliferative disorders (LPDs)

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Animal</th>
<th>Disease</th>
<th>Pathological mechanism</th>
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<tbody>
<tr>
<td><em>Theileria parva</em></td>
<td>Cattle and Cape buffalo</td>
<td>T-cell LPDs</td>
<td>Overexpression of casein kinase II</td>
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<tr>
<td>Avian leukosis virus (AVL)</td>
<td>Birds</td>
<td>AVL-induced B-cell lymphoma</td>
<td>c-myec activation</td>
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<tr>
<td>Parvovirus</td>
<td>Minks</td>
<td>Aleutin disease (B cell)</td>
<td>Persistent infection</td>
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cells or donor-derived EBV-specific cytotoxic T cells has been shown to be curative for bone marrow transplant patients with EBV associated with PTLD [36].

EBV-associated LPDs have also been observed infrequently in other settings of acquired immunosuppression such as rheumatoid arthritis, where a modest increase in the risk of developing LPDs has been observed [13]. A potential association between rheumatoid arthritis and LPDs was suggested by studies that showed a reduced ability of T cells to control EBV infection in patients with rheumatoid arthritis and in other related rheumatic diseases [13, 37]. The effect of this lack of control in vivo is the increase in the number of circulating EBV-infected B lymphocytes. It is well established that further immunosuppression of these patients, such as by treatment with methotrexate, may play a role in the etiology of LPDs of these patients by further decreasing the immune control of the EBV, and it is also known that these lymph-

Table 2. Proposed classification of antigen- and/or immune-driven lymphoproliferative disorders (LPDs)

<table>
<thead>
<tr>
<th>II. Infection related</th>
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<tbody>
<tr>
<td>1. Virus-associated LPD</td>
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<tr>
<td>A. Epstein–Barr virus (EBV)-associated LPD</td>
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<tr>
<td>i. Immunodeficiency-related, EBV-associated LPD</td>
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<tr>
<td>a. Post-transplant LPD (organ transplant-related)</td>
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<tr>
<td>b. Acquired immunodeficiency-related LPD</td>
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<td>c. Primary immunodeficiency-related LPD</td>
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<td>ii. LPD without overt immune defect</td>
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<tr>
<td>a. Burkitt’s lymphoma</td>
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<tr>
<td>b. Hodgkin’s disease</td>
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<td>c. Natural killer LPD</td>
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<tr>
<td>B. Human T-cell leukemia virus (HTLV) type I-associated LPD</td>
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<tr>
<td>i. Adult T-cell leukemia/lymphoma</td>
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<td>C. HTLV-II-associated LPD</td>
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<tr>
<td>i. T-cell lymphocytosis</td>
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<td>ii. ‘Atypical’ hairy cell leukemia</td>
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<td>iii. Large granular lymphocytosis</td>
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<td>D. Human herpesvirus 8-associated LPD</td>
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<tr>
<td>i. Primary effusion lymphoma</td>
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<tr>
<td>ii. Castleman’s disease</td>
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<td>E. Hepatitis C virus-associated LPD</td>
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<tr>
<td>i. Essential mixed cryoglobulinemia</td>
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<tr>
<td>ii. Other lymphomas</td>
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| 2. Bacteria-associated LPD |
| A. Helicobacter pylori-associated marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) |
| B. Borrelia burgdorferi-associated marginal zone B-cell lymphoma of MALT or immunocytoma |
| C. Immunoproliferative small intestinal disease |
| D. Pyothorax-associated lymphoma |

| 3. Parasite-associated LPD |
| A. Fasciola- and Anisakis-associated intravascular lymphomatosis |

<table>
<thead>
<tr>
<th>II. Immune-related LPD</th>
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<tbody>
<tr>
<td>1. Sjogren’s syndrome-associated marginal zone B-cell lymphoma of MALT</td>
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<td>2. Gluten sensitivity or enteropathy-associated T-cell lymphoma</td>
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<tr>
<th>III. Infection- and/or immune-related LPD</th>
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<tr>
<td>1. Gamma/delta T-cell lymphoma</td>
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<td>2. T-cell large granular lymphocytosis</td>
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<tr>
<td>3. Other extranodal marginal zone B-cell lymphoma of MALT</td>
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| IV. Others (e.g. drug-associated LPD) |

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1597
oid lesions frequently regress after withdrawal of methotrexate therapy [13, 37].

b. Acquired immunodeficiency-related LPD. HIV-infected individuals are known to have increased risk of developing NHLs, usually of high-grade B-cell type with frequent extranodal involvement, particularly involvement of the central nervous system (CNS) [4]. Occasional cases of T-cell NHLs have also been reported [38]. The collective information gained from many studies on AIDS-associated NHLs indicates that there are two main groups of AIDS-related lymphomas. The first are the large cell lymphomas with immunoblasts. These lymphomas are usually EBV-positive and display either the latency type II, or latency type III form of EBV infection. These lymphomas are believed to be associated with more severe impairment of the immune system and may be similar to PTLDs. The majority of the CNS lymphomas probably belong to this group. The other group is the Burkitt-type lymphomas. These lymphomas are associated with EBV in a smaller proportion of cases and the virus latency established in these lymphomas is more restricted. These lymphomas may be comparable to sporadic Burkitt’s lymphomas seen in immunocompetent individuals [14, 39].

c. Primary immunodeficiency-related LPD. Increased frequency of LPDs has been observed in primary immune defects syndrome [40–46]. LPDs observed in these patients include lymphoid hyperplasia, atypical lymphoid hyperplasia and NHLs, including high-grade and Burkitt’s lymphomas [41–43]. Progression from polyclonal to monoclonal disease has been suggested [47]. Additionally, different monoclonal EBV genomes in different tumor sites suggest a multiclonal origin in some cases [40].

ii. LPD in patients without overt immune defects.

a. Burkitt’s lymphoma. EBV DNA and some viral gene products are known to be present in virtually all cases of endemic Burkitt’s lymphoma, while only a minority of sporadic cases in the Western world are EBV-positive [48, 49]. EBV-positive Burkitt’s lymphoma cases have a very restricted form of latency, which is usually maintained with expression of F promoter–driven EBNA-1 and of the EBERs (latency I) [50]. The presence of this virus in virtually all endemic cases suggests an important role for this virus in the development of endemic Burkitt’s lymphoma. However, its absence from most sporadic Burkitt’s lymphoma cases indicates that its function can be substituted by other factors. In all EBV-positive Burkitt’s lymphoma cases the viral genome is monoclonal, indicating that the virus infection occurred before expansion of the malignant cell population [51]. All cases of Burkitt’s lymphoma, irrespective of their EBV status, display characteristic chromosomal translocation involving the c-myc oncogene on chromosome 8 and immunoglobulin genes on chromosomes 2, 14 or 22 [50]. Molecular studies have shown that the sites of the breakpoints on chromosome 8 differ between EBV-positive endemic cases and EBV-negative sporadic cases. Since EBNA-1, the only latent viral protein expressed in the endemic Burkitt’s lymphoma, does not belong to the classic transformation-associated viral proteins, it has been suggested that EBV in Burkitt’s lymphoma might simply be the initial stimulus to B-cell proliferation and likely to increase the possibility of chromosomal translocation [50]. Some recent studies have raised the possibility that EBNA-1 alone may be able to induce lymphomas [11]. EBNA-1 is the only EBV virus latent protein that is known to escape the
EBV-specific CTLs, ultimately leading to a mechanism for escaping immune surveillance [52, 53].

b. Hodgkin’s disease. The epidemiological and pathogenic association of classic HD with EBV has been well established. EBV sequences have been detected in 40% of the cases in the West and 80% of the cases in the developing world [54, 55]. The key findings supporting an etiological association of EBV with HD was the detection of the viral genome and virally encoded proteins in the Reed–Sternberg cells. The analysis of the EBV genome revealed that HD had clonal EBV episomes. This clonality indicates that HD develops from a single EBV-infected cell [56].

c. Extranodal natural killer/T-cell lymphoma, nasal type. Extranodal natural killer/T-cell lymphoma, nasal type, is almost always associated with EBV infection [57, 58]. These entities are most commonly seen among Asians, which suggests racial predisposition to the disease [57, 58]. These disorders have been described under a number of terms, reflecting its locally destructive clinical behavior (lethal midline granuloma) [59], polymorphous cell composition (polymorphic reticulosis) [60] or its tendency for angio invasion (angiocentric lymphoma) [61, 62].

B. Human T-cell leukemia virus type I-associated LPD.

i. Adult T-cell leukemia/lymphoma. Human T-cell leukemia virus type I (HTLV-I) was the first pathogenic retrovirus discovered in humans and is the etiological agent for adult T-cell leukemia/lymphoma (ATLL) and tropical spastic paraparesis [63, 64]. ATLL is a mature T-cell leukemia/lymphoma, most often of CD4 phenotype, that occurs in a very small percentage (2–5%) of HTLV-I-infected people within their lifetime [65]. The estimated average time between HTLV-I infection and malignancies is 20–30 years [66]. Epidemiological data indicate that ATLL develops mainly in individuals infected at birth, and suggest that age at onset of viral infection may be important in the development of leukemia [65–67]. The mechanism of leukemic transformation by HTLV-I infection is unclear. The virus does not contain any classical oncogenes and does not insert at specific sites within the host genome, and it is believed that the mechanism of leukemic transformation by this virus involves HTLV regulatory proteins [68]. The Tax protein, encoded by HTLV-I, serves as a potent transcriptional activator of its long terminal repeat, as well as of cellular genes such as interleukin (IL)-2, IL-2 receptor alpha (IL-2Rα), parathyroid hormone-related protein, granulocyte—macrophage colony-stimulating factor (GM-CSF), c-fos and NF-kB/KBF1, suggesting that this promiscuous trans-activating activity of Tax is likely to be the mode of HTLV transformation [69–74]. Expression of Tax has been shown to transform several types of cells in vitro, including primary human CD4+ lymphocytes [75]. The clinical course of ATLL compromises at least four different subtypes, i.e. acute, chronic, lymphomatous and smoldering, depending on the extent of the disease and serum calcium level [8, 65, 76]. The clinical course of established ATLL is rapidly aggressive, with a mean survival of 6 months. Rare cases of spontaneous remission of ATLL have been described [77].

C. HTLV-II-associated LPD.

i. T-cell lymphocytosis. Lymphoid diseases associated with HTLV-II are less well known than HTLV-I; most people known to be infected are asymptomatic carriers, although some will have mild T-cell lymphocytosis. As opposed to HTLV-I, HTLV-II appears to preferentially infect CD8+ cells [78].

ii. iii. ‘Atypical’ hairy cell leukemia and large granular lymphocytosis. Rare cases of lymphoid disorders, mainly ‘atypical’ hairy cell leukemia and large granular lymphocytosis (LGL), have been linked to HTLV-II, and this appears to be a rare complication of this virus [79–82].

Molecular pathology of HTLV-II infection is less well known, but appears to be similar to HTLV-I [78].

D. Human herpesvirus 8-associated LPD.

i. ii. Primary effusion lymphoma and Castleman’s disease. Human herpesvirus 8 (HHV-8) is a newly described human herpesvirus that exhibits homology to herpesvirus saimiri (HVS) and EBV. HHV-8 is closely associated with three proliferation disorders in HIV-infected patients: Kaposi’s sarcoma, primary effusion lymphoma and multicentric Castleman’s disease [83–87]. The high prevalence rate of this virus in these lesions suggests that HHV-8 is necessary in the pathogenic processes of these diseases. The exact pathological mechanism of the transforming capacity of this virus remains uncertain; however, it is believed that some HHV-8 viral genes are homologous to cellular genes involved in cell proliferation (viral IL-6 and G-protein-coupled receptor) and transformation (viral bcl-2 and viral cycline) [88–92]. Persistent hypergammaglobulinemia and polyclonal plasmacytic infiltrates have been observed to proceed to the development of lymphomas associated with this virus [93]. HHV-8-associated multicentric Castleman’s disease occurs predominantly in patients with AIDS, but also in HIV-negative patients [84–86]. This finding suggests a direct role of HHV-8 in the development of multicentric Castleman’s disease with HIV-induced immunosuppression serving as a secondary factor. The detection of this virus has been shown by some investigators in multiple myeloma and anecdotally in cases of angioimmunoblastic lymphadenopathy and germinal center hyperplasia [94, 95].

E. Hepatitis C virus-associated LPD.

i. ii. Essential mixed cryoglobulinemia and other lymphomas. HCV is known to be associated with several extrahepatic manifestations, most of which are immunologically mediated [96]. The association between HCV infection and essential mixed cryoglobulinemia (MC), which is now considered to be a low-grade NHL, is unequivocal [10, 97–99]. Antibodies to HCV and HCV RNA have been found in up to 98% of patients with MC [100]. HCV has no DNA intermediate and cannot integrate into the host genome; therefore, it cannot be considered as an oncogenic virus. However, it has recently been demonstrated that both HCV non-structural protein NS3 and HCV core protein are capable of cell transformation in nude mice, and that HCV core protein is able to regulate cellular protooncogenes at the transcriptional level, indicating
that the persistence of HCV in the immune system could result in chronic stimulation of B-cell secreting cryoglobulin, probably leading to their progressive clonal expansion [101, 102].

HCV infection appears to be found in each subtype of NHL, but available data from several studies suggest that some subtypes are more likely to be associated with this infection—lymphoplasmacytoid lymphoma/immunocytoma appears to be the most frequent. Other histological subtypes were recently reported as possibly being associated with related to HCV infection, including follicle center and marginal zone lymphomas, and primary hepatosplenic lymphomas [103].

Studies have demonstrated that HCV is able to infect and replicate within peripheral blood mononuclear cells including B-lymphocytes, as well as CD34+ hematopoietic progenitor cells [99, 104, 105].

Additionally, HCV RNA or proteins have been found among epithelial cells of a parotid NHL with MC, and in bone marrow and lymph node biopsy specimens of patients with B-cell NHL [105, 106].

Regression of monoclonal B-cell expansion has been demonstrated in patients with MC and NHL in whom the HCV virus was cleared following α-interferon treatment [107–109]. The use of this agent should be considered as a therapeutic option for HCV-related low-grade NHL [110].

A summary of all viruses implicated in antigen- and/or immune-driven LPDs is depicted in Table 3.

**2. Bacteria-associated LPD**

**A. Helicobacter pylori-associated marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.** The relationship between *Helicobacter pylori* infection and marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT) of the stomach is well described [111]. *Helicobacter pylori* has a small genome and it lives primarily in the human stomach, and in order for it to survive in the harsh gastric milieu, most of its enzymatic pathways are continually switched on [112]. The micro-organism can be found in gastric mucosa of nearly all cases of MALT lymphoma [113]. The response of low-grade B-cell gastric MALT lymphoma to stimulating strains of *H. pylori* is dependent on *H. pylori*-specific T cells and their products [114].

Progression of *H. pylori*-associated chronic gastritis through polyclonal lymphoid hyperplasia to monoclonal low-grade NHL has been well documented by histological and molecular studies [12, 115].

MALT gastric lymphoma is characterized by an indolent clinical course and generally remains localized at the site of origin for prolonged periods without systemic spread [116].

Regression of low-grade gastric MALT lymphoma has been described after eradication of *H. pylori* infection with antibiotic therapy, where complete resolution of early stage lesions have been observed [5, 117].

In patients with higher tumor stage, treatment with single-agent chemotherapy or radiation alone induces high remission rates [118, 119]; however, irradiation of *H. pylori* infection should be considered in all cases to avoid disease recurrence.

**B. Borrelia burgdorferi-associated marginal zone lymphoma of MALT or immunocytoma.** Evidence of ongoing somatic hypermutation and isotype switching has been demonstrated in some cases of primary cutaneous B-cell lymphomas, features that are shared with extracutaneous marginal zone B-cell lymphoma of MALT [120].
The association of primary cutaneous immunocytoma/marginal zone lymphoma of the skin with {Borrelia burgdorferi} has been well described [6]. Immunohistological studies in such cases were indicative of progression of polyclonal lymphocyte population to monoclonal phase. This lymphoma has good overall prognosis and is known to be responsive to systemic antibiotic therapy and local measures [6, 121].

C. Immunoproliferative small intestinal disease. Immunoproliferative small intestinal disease (IPSID) is a prevalent small intestinal lymphoma in the Third World, where frequent infantile infections, enteritis and high incidence of intestinal parasitic infections are common [122–124]. This disease is more frequently seen in Mediterranean areas, frequently affecting Arabs and non-European Jews, which also suggests an element of genetic susceptibility [122, 125, 126]. Association with a certain human leukocyte antigen phenotype has been described [127, 128]. The specific bacterial or non-bacterial infectious agents have not been determined, and it is likely that multiple antigenic stimulation promotes the trigger for clonal evolution of this disease [124, 129]. The polyclonal lymphoplasmacytic infiltration of the intestinal mucosa and regional mesenteric lymph nodes is likely to represent a response of the elementary tract immune apparatus to protracted luminal antigenic stimulation, which ultimately leads to progression and growth of monoclonal immunocytes synthesizing the anomalous α-chain protein [130, 131]. Early IPSID presents with steatorrhea and weight loss, and has benign-looking antibiotic responsive lesions that frequently progress to high-grade lymphoma with variable clinical course, which is probably related to persistent antigenic challenge, genetic factors and oncogene activation [132–135]. The non-malignant nature of the early pre-lymphoma of this stage in the vast majority of patients with IPSID is supported by spontaneous regression or antibiotic-induced remission [133–135]. Monoclonality has also been demonstrated in benign-looking mucosal plasma cells in early stages of the disease [129, 136]. Reports documenting chromosomal aberrations in the intestinal lymphoma cells support the role of secondary genetic events in the evolution of this disease [137]. Although advanced cases of this disease seems to be less responsive to antibiotic therapy, successful remission has been reported in patients with advanced disease who had failed chemotherapy treatment [134].

D. Pyothorax-associated lymphoma. Pyothorax-associated lymphoma develops in patients with long-standing pulmonary tuberculosis, especially those with artificial pneumothorax [138, 139]. In Japanese patients, this type of lymphoma has been reported almost exclusively in patients who had an artificial pneumothorax for pulmonary tuberculosis [138, 139]. Pyothorax-associated lymphoma with clear evolution from T-cell-rich lymphoid infiltrate to overt B-cell lymphoma in association with EBV have been well described [140].

Fukayama et al. [141] suggested that in the presence of pneumothorax, immunocompetent cells may not be able to enter the pleural cavity, and this may contribute to the pathology of this entity.

3. Parasite-associated LPD

A. Fasciola- and Anisakis-associated intravascular lymphomatosis. Some parasitic infections have been reported to be associated with intravascular lymphomatosis (vide supra) [142].

II. Immune-related LPD

1. Sjögren’s syndrome-associated marginal zone B-cell lymphoma

Sjögren’s syndrome is a disease characterized by lymphocyte infiltration of salivary and lacrimal glands leading to a progressive destruction of these glands by production of autoantibodies [143]. The risk of developing NHL in Sjögren’s syndrome was estimated to be 44 times greater than observed in comparable normal population [144]. NHL in Sjögren’s syndrome patients occurs preferentially in salivary glands, in other mucosa-associated lymphoid tissues and in lymph nodes. The evolution from benign to malignant NHL is a multistep process, the exact underlying molecular evidence of which is still unknown; however, some of the translocations or mutations of oncogenes or tumor suppressor genes described in other lymphomas have been described in Sjögren’s syndrome-associated lymphoma [145, 146]. These lymphomas are usually of low-grade marginal zone type, and are not known to be associated with viruses known to be present in other types of lymphomas [147].

2. Gluten sensitivity or enteropathy-associated T-cell lymphoma

Patients with celiac disease have an increased incidence of intestinal lymphoma that arises from intraepithelial T lymphocytes (IEL) [148]. The relative risk of lymphoma in patients with celiac disease is a subject of debate, with most estimates ranging from 40- to 100-fold greater than individuals without celiac disease [149]. Strict adherence to a gluten-free diet is known to substantially eliminate the risk of developing intestinal lymphoma. A 10-year follow-up study in Finland of 335 patients with gluten sensitivity who were highly compliant with dietary treatment showed no increase in the frequency of lymphoma among patients compared with age-matched controls [150]. Patients with celiac disease may present with a history of several months to years of abdominal pain and weight loss, and a small proportion of patients have a history of celiac disease dating back to childhood, but many patients with gluten-sensitive enteropathy may have subclinical or only mildly symptomatic disease [151–153]. Enteropathy-associated T-cell lymphoma (EATL) commonly occurs in the jejunum, either alone or in combination with multiple other sites in the gastrointestinal tract. EATL is considered to be a T-cell lymphoma that arises from IEL [154]. Complicated forms of celiac disease tend to be unresponsive to a gluten-free diet, and have a higher likelihood of having an oligoclonal or monoclonal population of lymphocytes [155]. The collective information from several clinical studies confirms the progression of polyclonal lymphoid population of enteropathic bowel to low-grade and
high-grade lymphomas, which sometimes also involve the liver, spleen and bone marrow [154, 155].

III. Infection- and/or immune-related LPD

1. Gamma/delta T-cell lymphoma

The gamma/delta (γδ) T cells make up 5% of T cells in the peripheral blood and lymphoid tissues [156]. The exact role of γδ T cells in the course of infectious diseases and pathogenesis of autoimmunity has been inferred from their expansion in skin lesions in leprosy and leishmaniasis, in blood in malaria, in synovial fluid in rheumatoid arthritis and in jejunal mucosa in celiac disease [157]. It is also well known that γδ T cells are expanded in a variety of other human diseases characterized by chronic inflammation and granuloma formation and in some viral infections [157].

Post-thymic T-cell lymphomas bearing γδ-type of T-cell receptors on the cell surface are rare. Three distinct groups have been recognized: the hepatosplenic form, the cutaneous form and the nasal form [158]. Increased numbers of γδ T cells have been found in peripheral blood of renal allograft recipients [159]. Among the rare occurrence of non-B-cell phenotype of lymphoma seen in immunosuppressed patients, the γδ phenotype have been infrequently reported [160–162]. Clonal evolution has been demonstrated in several γδ T-cell lymphomas in immunosuppressed patients that have been followed up longitudinally, with acquisition of karyotypic abnormalities at the time of blastic transformation [157].

2. T-cell LGL

Clonal expression of T cells with LGL morphology is frequently associated with autoimmune manifestations [163]. Quantitative abnormalities of large granular lymphocytes have also been observed as a transient phenomena associated with viral infections or chronic LPDs characterized by chronic neutropenia [163]. This disease is known to have an indolent course in the majority of patients, with frequent spontaneous remissions and response to immunosuppressive therapy [163–165]. It is conceivable that antigen activation in addition to lymphocyte secretion could lead to LGL in vivo. Both polyclonal and monoclonal cases have been reported. The development of karyotypic abnormalities with evolution to acute phase has been reported in rare cases [166].

3. Other extranodal marginal zone lymphoma of MALT

Extranodal marginal zone lymphoma of MALT tends to be a localized disease, and it is conceivable that a large number of these localized extranodal lymphomas arise as a result of some pre-existing local or tissue-restricted antigenic or immunological factor [167, 168].

Typical association of extranodal marginal zone lymphoma of MALT has been described after Hashimoto’s thyroiditis (thyroid gland) [169], inflammatory lung conditions (lung) [170–172], reactive and inflammatory conditions (orbit) [173], and other previously mentioned conditions: H. pylori (gastric), B. burgdorferi (skin) and HCV infection (different sites) [171, 172].

Clonal evolution has been described in most of these lymphomas, and these lymphomas remain localized to the site of original disease with low likelihood of spread to the other sites [167, 168].

IV. Others

Drug-associated lymphoid proliferation

The rare association of phenytoin therapy and lymphoadenopathy in the form of pseudolymphoma or malignant lymphoma has been described in several small series and case reports [7, 174–176].

Immunoblastic hyperplasia is a prominent feature in most cases. In cases where sequential biopsies were obtained, clear evidence of progression from paracortical hyperplasia to malignant lymphoma has been documented [176, 177].

Conclusion

In this review, we attempted to present an etiology-based classification of a group of LPDs, believed to be instigated from transformation of polyclonal population of normal lymphocytes to clonal, neoplastic disorders. We referred to this group as antigen- and/or immune-driven lymphoproliferative disorders (AID-LPD). This group of disorders and its related antigenic and immunological perpetrators is ever expanding.

Finally, periodic review and update to incorporate new information into this classification is pivotal. Because the technology of genetic and immunological analysis is moving rapidly, it is very likely that the advances in our understanding of the molecular and immunopathology of the individual entities of this classification will necessitate continuous revisions.

References


