Rheumatoid Factors in Hepatitis B and C Infections: Connecting Viruses, Autoimmunity, and Cancer

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ABSTRACT: Serum rheumatoid factors are autoantibodies of different isotypes directed against the Fc fraction of immunoglobulin G (IgG) and represent paradigmatic autoantibodies that have been largely used in clinical practice for decades. Traditionally IgG has been associated with rheumatoid arthritis and more recently included also in the classification criteria for Sjögren's syndrome. Researchers have established that rheumatoid factors are positive in a variety of infectious, autoimmune, and neoplastic disorders, thus requiring a comprehensive evaluation of seropositive patients. Of note, hepatitis B and C viruses represent a crossroad that includes the high rheumatoid factor seroprevalence and chronic inflammatory disease, as well as progression to non-Hodgkin's lymphomas. Chronic antigen stimulation is the likely common ground of these processes and rheumatoid factors may represent mere bystanders or drivers of pathology. Mixed cryoglobulinemia and lymphoproliferative disease are prime examples of the deleterious effects of rheumatoid factor-B cell activity, possibly associated with hepatitis B and C. More importantly, they show a clear association in a physiological host response to infection, chronic inflammation, and the slide toward autoimmunity and malignancy. The association between hepatitis B and C infections and the appearance of serum rheumatoid factors is further supported by prevalence data, which support a coexistence of these markers in a significant proportion of cases, with viral infections being frequent causes of rheumatoid factors in patients without a rheumatic condition. We provide a comprehensive overview of the known connections between hepatitis B and C infections and rheumatoid factors.

IMAJ 2019; 21: 480–486

KEY WORDS: cryoglobulinemia, hepatitis B, hepatitis C, rheumatoid factor, lymphoproliferative disorders

Rheumatoid factors (RF) are autoantibodies directed against the Fc region of immunoglobulin G (IgG), which are recognized as the serological marker for rheumatoid arthritis (RA). Since their discovery in 1940, RF have been extensively studied in association with autoimmune phenomena, as well as in the context of host response to chronic infections. More recent research implicates B cells producing RF in the pathogenesis of specific lymphoproliferative disorders. One setting in which these aspects are recapitulated is the hepatitis C virus (HCV) and to a lesser extent hepatitis B virus (HBV) infection where RF appear to be an ever-present bystander at the crossroads of host resistance, autoimmunity, and malignancy stemming from the viral infection.

HCV is an enveloped, single-stranded RNA virus with a genome consisting of approximately 10,000 nucleotides that encode a polyprotein (3000 amino acids) later processed by host cells and viral enzymes into 10 structural and non-structural (NS) proteins coined NS2, NS3, NS4A, NS4B, NS5, and NS5B. The structural proteins include a core protein and envelope glycoproteins E1 and E2 [1]. As many as 150 million people worldwide are infected. Approximately 50–80% of those diagnosed with acute hepatitis C (commonly asymptomatic) will develop a chronic infection, which may result in cirrhosis and hepatocellular carcinoma. This finding contrasts to HBV infection in which acute hepatitis is followed by an asymptomatic carrier state is the most common outcome of the infection, and fewer than 5% of adults develop chronic hepatitis. The viron consists of partially double-stranded circular DNA, replicative enzymes, nucelocapsid core (HBcAg, HBeAg), and envelope glycoproteins (HbsAg), which along with their complementary antibodies (anti-HBc, ant-HBs) represent the signature markers of the infection. The prevalence of the virus in the population is typically lower than that of HCV, although high-prevalence areas exist such as in China for HBV and Egypt for HCV [1,2].

In spite of the hepatotropic nature of HBV and HCV, as many as 17% and 40% of patients will develop extrahepatic manifestations, respectively, many of them immune-mediated in nature, such as arthritis, glomerulonephritis, sicca syndrome, and vasculitis. Moreover, associations with lymphoproliferative disorders, such as mixed cryoglobulinemia and non-Hodgkin's lymphoma, are well-established. However, their occurrence is less common in HBV [3,4]. A distinctive feature of both is the association with the presence of autoantibodies traditionally found in systemic (antinuclear antibodies and rheumatoid factors) and hepatic autoimmune diseases (anti-LKM1, anti-SM, and anti-mitochondrial antibodies) [5]. RF also has a particularly high

prevalence in HCV infected patients, approximately 40–76% in HCV seropositive patients [6], while rates between 20% and 75% can be obtained for RF in HBV positive patients [7].

THE CONUNDRUM OF RHEUMATOID FACTORS

The high reported prevalence of RF in the general population contradicts the hypothesis that these autoantibodies are indeed pathogenic. A recent study involving 500,000 participants found that approximately 21% were seropositive for rheumatoid factors [8], although previous works reported lower estimates of approximately 1.3–4% in the general population [9] with the notable outlier of Pima Indians. In this population, the prevalence was reported to be over 30% [10]. Genetic factors are suspected to account for discrepancies among populations, but the study of the Northern American tribes concluded that RF are distributed in a fashion incompatible with a hereditary pattern [10]. Since then, twin studies have shown a clear association between HLA-DR4 alleles and RF production. RF prevalence in the Finnish population also showed significant regional differences correlating with the hypothesis that environmental factors are the likely driver of RF appearance [9].

A transient RF production has been associated with viral, bacterial, and parasitic infections and is believed to represent a physiological response, as the evidence suggests, and induced through antibodies bound to highly ordered, repetitive antigens as opposed to monomeric or oligomeric antigens. Most infectious agents expose such epitopes on their surface. RF secretion by B lymphocytes requires simultaneous stimulation of B-cell receptor by an IgG linked to an antigen and Toll-like rReceptor stimulation by an epitope, which is sustained by their interaction with immune complexes (ICs) [11]. This view is supported by experimental studies that demonstrate how RF contribute to the clearance of immune complexes (ICs) in mice stimulated with lipopolysaccharide (LPS), with titers increasing proportionally to the level of ICs. Patients presenting with infectious exacerbations of cystic fibrosis manifest elevated titers if IgM independent of total IgM and correlated with levels of circulating ICs [12].

Most likely RF lead to ICs clearance by increasing their size and facilitating the engulfment by phagocytes. In addition, B cells producing rheumatoid factors can act as competent antigen presenting cells [13]. A key factor that contributes to the RF seroprevalence is the duration of infections, as chronic carriers for HBV or HCV are generally characterized by high prevalence of RF. This thesis is perhaps best illustrated by a study conducted on syphilis carriers where patients with Treponema infections, had rheumatoid factors rates increasing with the primary, secondary, and tertiary stages [9].

A distinction should be made between low-affinity and high-affinity RF, with the former referred to as 'natural' because of occurrence in healthy individuals. It is predominantly an IgM-type antibody produced by CD5+ B-cells, independent of T-cell function. In addition, low-affinity RF can raise transiently during microbial infections and indeed similar antibodies were obtained in animal models in response to stimulation with LPS or Epstein–Barr virus [14]. High-affinity RF include IgM, IgG, IgA, and IgE isotypes, and IgA antibody in particular, are characteristic of the synovial fluid of RA patients. These antibodies are monoreactive and produced in a T-cell-dependent manner by CD5-negative B2 cells while being traditionally associated with other autoimmune conditions such as Sjögren's syndrome. In contrast to low-affinity RF, genes encoding the V regions of high-affinity RF contain a number of somatic point mutations [14].

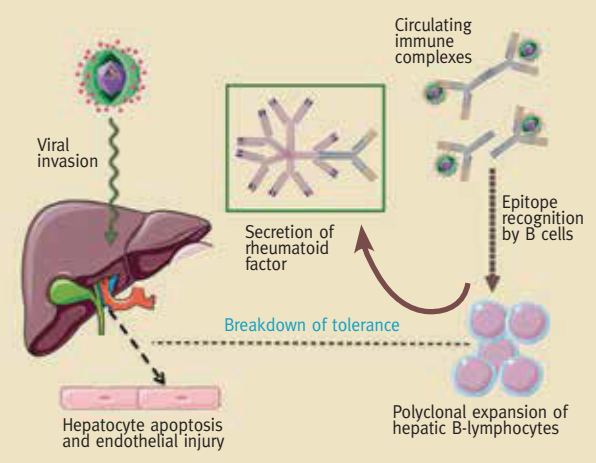
LIVER INJURY AND THE SLIDE TOWARD AUTOIMMUNITY

Although the production of RF in the setting of either HBV and HCV infection is likely to be a part of the normal response to circulating ICs, the presence of RF may be attributed, at least in part, to non-specific liver damage. Study of individuals with alcoholic liver disease consistently report RF positivity, which cannot be explained by infections, autoimmunity, or neoplasia [15]. The liver is considered to be an immune-privileged organ as the immune response is carefully regulated to avoid continuous stimulation by antigens entering the portal circulation [16]. Research evidence in animal models demonstrates that damage to endothelial lining of the organ may lead to the breakdown in tolerance of hepatic B-cells, as illustrated in Figure 1. In the setting of a murine anti-fas-antibody-mediated liver injury model, Newkirk and colleagues [15] have demonstrated the RF humoral response in the absence of a microbial stimulus. Moreover, immunohistological studies of HCV-infected livers show an accumulation of lymphocytes around the portal tracts that organize into follicle-like structures containing germinal centers similar to other lymphoid organs, an occurrence that has been documented to a lesser extent in HBV [17]. Moreover, in the context of HCV, the spontaneous production of RF by clonally expanded hepatic B cells has been demonstrated [18].

Hepatitis B and C infections are important confounding factors in the diagnosis of autoimmune disorders such as rheumatoid arthritis and Sjögren's syndrome due to the high prevalence of rheumatoid factors in infected subjects and the inclusion of these autoantibodies in the classification criteria of both conditions

Despite the provided data, the occurrence of RF in HBV and HCV infections remains somewhat problematic as the RF have been a part of the classification criteria for RA since 1956 and retain their role as disease markers in the recent ACR/EULAR recommendations and criteria, although in recent years, it lost some of the spotlight to the more specific and clinically meaningful anti-cyclic citrulinated peptide (CCP) antibodies. However, various infections and autoimmune disorders

Figure 1. A simplified model of rheumatoid factor secretion in chronic hepatitis B virus and hepatitis C virus infections [created using images adapted from Servier Medical Art]. Hepatic viral invasion provides a dual stimulus for the initial rheumatoid factor response. Hepatic injury results in cell apoptosis and endothelial damage that drive the breakdown of the organ immune tolerance, expose patients to antigens entering from the portal circulation, and induce them to polyclonal expansion of hepatic B cells as well as rheumatoid factor secretion in animal models and a possible non-specific pathway for autoantibody secretion in liver diseases. ICs including viral particles and host antibodies are able to elicit the infection-related rheumatoid factor response that persists during chronic disease. It is likely that both non-specific liver injury and sustained viral stimulation are able to drive the secretion of rheumatoid factor in this setting



(such as Sjögren's syndrome) that are characterized by high RF serum prevalence may present with RA-like symptoms [19] and prevalence rates of RF are illustrated in Table 1. The presence of such a confounding factor poses a diagnostic challenge, which is accentuated by the high frequency of specific viral infections such as HBV and HCV.

HBV-associated arthritis may present in two modes depending on whether HBV infection is acute or chronic, in conditions such as polyarteritis nodosa. In the first case, arthralgia with serum-like sickness typically precede the development of jaundice but in a minority of cases patients may manifest a transient RA-like polyarthritis [19]. Furthermore, there are reports of post-HBV vaccine RA-like syndrome, which may fulfill the ACR criteria [20]. Similarly, HCV is also associated with symmetrical chronic polyarthritis reminiscent of RA. The high prevalence of IgM RF in HBV and HCV infection [Table 1] makes RF poor diagnostic tools for differentiating between diseases, and consequently, studies have been conducted to verify the presence of other RF isotypes in the blood of non-arthritic HCV and HBV patients. The presence of specific immunoglobulins is variable, with IgG, IgM, and IgA prevalence rates of 52%, 26%, and 14%, respectively [21]. Similarly, in HBV patients IgG, IgM, and IgA RF

Table 1. Prevalence of rheumatoid factor isotypes in specific clinical conditions [6,21,22,38-40]

	RF IgM	RF IgG	RF IgA	Overall
General population	7.1%	4.5%	4.5%	1–30%
RA	65%	14%	51%	70–90%
Sjögren's syndrome	36%	31%	23%	75%
MCTD	48%	38%	33%	50–70%
Chronic HBV	19%	21%	29%	20–75%
Chronic HCV	26%	52%	14%	40–76%
Liver cirrhosis	–	–	–	25%
Healthy › 50 years of age	–	–	–	10%
Healthy › 70 years of age	–	–	–	10–25%

HBV = hepatitis B virus, HCV = hepatitis C virus, Ig = immunoglobulin, MCTD = mixed connective tissue disease, RA = rheumatoid arthritis, RF = rheumatoid factor

were positive in 21%, 19%, and 29% of the tested sera [22]. The high prevalence of the IgA isotype RF is particularly surprising, given its strong association with RA classically described in the literature. However, both articles found very low prevalence of anti-CCP antibodies, thus suggesting that they may represent the only marker to differentiate between RA and hepatitis-associated arthritis. As mentioned previously, natural rheumatoid factor response is marked by the secretion of low-affinity antibodies that do not exhibit isotype switching. Nonetheless, it was established that chronic antigen stimulation may lead to remodeling of rheumatoid factor response into somatically-mutated, high-affinity antibodies reminiscent of those encountered in RA [9]. It remains to be demonstrated what precise function these isotypes have in the disease as thus far only monoclonal IgM RF have been directly linked with the development of extrahepatic manifestations of HCV as is the case in mixed cryoglobulinemia (MC) [23].

MIXED CRYOGLOBULINEMIA IN CHRONIC HEPATITIS INFECTION

Cryoglobulins are immunoglobulin complexes that precipitate in vitro at temperatures below 4°C, and they are arrayed into 3 groups according to the clonality and antibody types present in the complex. Type I cryoglobulins consist of monoclonal IgM (or IgG) and they are characteristic of lymphoproliferative conditions such as Waldenström's purpura or multiple myeloma, thus being of hematological interest.

Type II cryoglobulins are a mixture of monoclonal IgM (with rheumatoid factors activity) and polyclonal IgG. Type III cryoglobulinemia has polyclonal antibodies of both isotypes in the same time. Types II and III are known as MC and type II in particular is predominantly (but not exclusively) associated with HCV infection [24], a prime setting for the research on the subject in the last decades. Although MC has been reported in HBV infection, the prevalence is considerably lower (2%) [3] and most of the evidence on this subject comes from studies in HCV.

Approximately 40–60% of HCV-positive individuals have detectable levels of type II cryoglobulins, but only a minority

will develop the characteristic clinical syndrome associated with the presence of cryoglobulins (i.e., small vessel, ICs-mediated vasculitis) [24]. The etiology of MC is most likely related to the natural history of HCV infection and various mechanisms have been proposed to explain its role in this condition. HLA polymorphisms (HLA-DR11). as well as metabolic and hormonal risk factors, have been proposed for MC but the disease likely arises due to viral antigens (particularly HCV core and E2) that provide a continuous immune stimulation. An example of such an interaction is the binding of HCV-E2 envelope protein to CD81 on human B-cells that triggers the c-Jun N-terminal kinase (JNK) pathway and leads to the proliferation of subset of B1 (CD5+) lymphocytes [25].

Another mechanism described in the literature is the HCV pairing with very low density lipoprotein (VLDL) then evoking a T-cell independent activation of B-lymphocytes and production of monoclonal RF. In addition, the VLDL model described by Agnello and colleagues [26], is thought to obscure the virus and allow it to enter cells while evading immune response with the VLDL-mediated transport of the virus supported by the upregulation of LDL receptors at sites associated with manifestations of type II MC, such as skin keratinocytes [26,27].

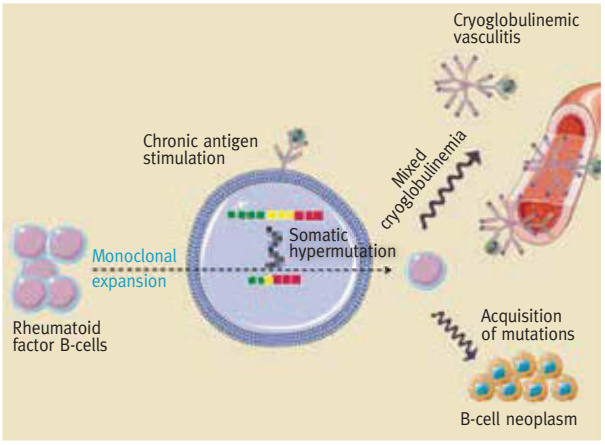
Irrespective of the precise mechanisms, HCV leads to the clonal expansion of B cell subsets guided by chronic antigen stimulation, even in the absence of MC. This mechanism is supported by the use of a restricted Ig heavy chain VDJ repertoire by observed B cell clones [28]. Notably, patients who harbor these proliferating clones do not seem to show any marked increase in circulating B cells. The expanded subsets of B lymphocytes are CD27+IgM+ non-clonally switched memory B cells secreting somatically mutated RF Ig [18] encoded by the V(H)1-69 variable gene. These B cells constitute up to 75% of circulating B lymphocytes (as opposed to 25% of memory-phenotype B cells in healthy subjects) in tested individuals. It has been postulated that such cells are a circulating variant of splenic marginal zone B-lymphocytes [29].

Patients affected by hepatitis C virus, and to a lesser extent hepatitis B virus, may develop cryoglobulinemia and non-Hodgkin's lymphoma, which are believed to be on a spectrum of manifestations caused by progressive rheumatoid factor-B cell expansion and mediated by chronic antigen stimulation

The pathogenesis of type II MC is unlikely to be a single-step process and is thought to arise through a number of transformations of RF-producing B-cells. For example, it is known that type III cryoglobulinemia with polyclonal IgM RF is reported in a number of anti-HCV positive patients. However, this condition is believed to represent a transition state, sometimes described as a new type-II-type-III mixed cryoglobulinemia variant- before the emergence of IgM RF characteristic of type II mixed cryoglobulinemia [30].

An alternative hypothesis for clonal expansion has been proposed based on investigations on the role of the IgG3 subclass,

Figure 2. Mixed cryoglobulinemia and and B-cell neoplasms: an overview of proposed mechanisms [created using images adapted from Servier Medical Art]. Chronic stimulation by viral antigens leads to monoclonal expansion of B-cell subsets producing rheumatoid factor. These cells are marked by somatic hypermutation in the variable region of the immunoglobulin gene. It is known that monoclonal rheumatoid factor are a component of MC that cause leukocytoclastic vasculitis in some individuals affected by chronic hepatitis B virus and hepatitis C virus infections. In selected cases, persistent immune stimulation leads to malignant expansion of monoclonal rheumatoid factor B-cells which acquire the appropriate mutations and then give rise to non-Hodgkin's lymphomas



an antibody strongly associated with immune stimulation. The results suggest that cryoglobulins are originally formed in two IgG classes. First, IgG1 RFs recognize the virus and activate IgG3, which are capable of precipitating immune complexes. Only later, due to the continuous antigen stimulation, are polyclonal IgM RF formed and undergo selection into IgM characteristic of the disease, as described in previous models. Basile et al. [31] suggested that the early identification of IgG3 RF in the sera of patients with HCV could be used as an early predictor of the development of MC and for the assessment for antiviral therapy eligibility [31].

While there is a paucity of data on the pathogenesis of MC in HBV infection, it is difficult to imagine a radically different immunological mechanism guiding it. Indeed, a study investigating MC in the context of HBV virus has demonstrated the clonal B-cell expansion of B-cells producing VH1-69-encoded antibody reminiscent of those seen in HCV. This finding is likely a result of chronic antigen stimulation, although data on the identity of such a molecule and its interaction with the host immune system leading to cryoglobulin production is lacking. Moreover, therapy with the

anti-viral therapy telbivudine is associated with the regression of HBV-associated MC [32].

The presence of cryoglobulinemia is not a ubiquitous feature of HCV and this finding can be explained by the existence of qualitatively distinct lymphoid cells in some individuals that have a lower ability to concentrate the microbial particles on their surface and consequently exhibit a weaker ability to replicate the virus [28]. Studies have supported a relationship between HCV replication, high RF activity, and expansion of monoclonal RF B cells. In addition, research investigating HCV endocytosis through LDL receptor (LDLr) has shown that the presence of the apoE2 allele correlates with a threefold increased risk of HCV patients developing MC [26,27].

MIXED CRYOGLOBULINEMIA AND MALIGNANCY

The first reports of a possible association between non-Hodgkin's lymphoma and HCV chronic infection came from epidemiological studies indicating a higher incidence of non-Hodgkin's lymphoma in Italian patients chronically infected with HCV. Despite conflicting figures coming from different regions, an extensive meta-analysis demonstrated a consistently increased risk of lymphoproliferative disorders in HCV carriers [4]. However, the link between HBV and non-Hodgkin's lymphoma has been studied less intensely even though it was first described in the same era of HCV-association. Since that time, it has been confirmed in various epidemiological studies.

Specific WA-Xid rheumatoid factors show a particularly strong association with cryoglobulinemia and non-Hodgkin's lymphomas and may be used as a predictor of these complications in patients with chronic hepatitis C virus infection

Low-grade marginal zone lymphoma at extranodal sites (liver, spleen, and salivary glands, which are uncommon at other sites) and diffuse large-b-cell lymphoma (DLCBL) are the most frequently encountered NHL variants, and they usually develop after a long-standing HCV infection (over 15 years), while HBV is associated predominantly with DLBCL [33]. Even if HBV was initially thought to be a mere association, it is now recognized that HCV is likely to be a causative NHL agent in a subgroup of patients as supported by the lymphoma remission in 75% of patients treated with HCV antiviral therapy. This is not dissimilar to lymphomas in chronic H. pylori infection or Sjögren's syndrome where chronic stimulation of the immune system has been implicated as a causative factor of neoplasia, while the removal or control of the inciting antigen tends to be curative [28]. There are no reports of NHL remission following HBV-treatments and this may well be seen as negative evidence for a causative association.

WA CROSS-IDIOTYPE

An analysis of multiple IgM RF from MC identified two major IgM RF cross-idiotype groups, namely WA and PO. WA are present in healthy subjects with no IgG reactivity, which is thought to arise only as the result of somatic mutations in the setting of chronic antigen stimulation [26], and the autoreactive variant may be unique to HCV infection in about 80% of cases of MC [34]. Unlike other IgM RF, WA cross-idiotype (Xid) does not manifest isotype switching and resembles natural antibodies though marked by the expression of particular VDJ segments. WA Xid has been implicated in the formation of cryoglobulins involved in systemic vasculitis of MC, and a proportion of HCV-related B-cell NHL are thought to originate from WA cells. Consequently, it was postulated that WA cells may be used as predictors of those complications in otherwise asymptomatic HCV-positive individuals and guide the assessment for antiviral therapy [26].

Various hypotheses have been proposed to implicate the viral pathogenesis of lymphomas and this connection remains uncertain, but evidence on the common pathogenesis comes from research on HCV-positive subjects and may also refer to HBV-related lymphoproliferation [33]. The direct viral induction has been demonstrated in vitro and HCV-induced (14:18) translocation and stochastic transformation with viral proteins driving the induction are mentioned as other possible mechanisms with varying amount of evidence in support. Agnello and Elfahal [27] suggested that WA IgM RF B cells as important players in the malignant transformation process, as shown in a study of 17 patients where 4 had NHL deriving from WA IgM RF B cells. Another piece of evidence comes from the single report of a patient with splenic lymphoma in which WA IgM RF cells accounted for 80% of lymphocytosis which regressed after antiviral therapy. These reports reveal an important link between chronic antigen stimulation, clonal RF B cell expansion and progression to malignancy, and theyhighlight the potential role of WA IgM RF in the risk of complications in HCV patients [27].

B-CELL NEOPLASMS IN HEPATITIS C VIRUS AND SJÖGREN'S SYNDROME

Sjögren's syndrome is a connective tissue disease affecting predominantly the salivary and lacrimal glands, but it frequently shows extra-glandular involvement and is associated with an increased risk of progression to NHL [4,35]. The association between Sjögren's syndrome and HCV is known and it is further demonstrated in a study of 1309 patients with Sjögren's syndrome and positive anti-HCV antibodies in 12% of cases [4]. In addition, chronic HCV infection may cause a sicca-like syndrome.

HCV has been shown to replicate in the epithelial cells derived from salivary glands of patients with Sjögren's syndrome [36]. Based on these observations, the positivity for anti-HCV antibodies is currently a negative prognostic factor in the classification of Sjögren's syndrome but the pathogenetic mechanisms are unclear. Lymphoproliferative diseases associ-

ated with Sjögren's syndrome share some similarities with those encountered in HCV patients, to the point where shared pathogenesis has been suggested for NHL in the context of both disorders [36]. Indeed, patients may present with a triple association of HCV, Sjögren's syndrome, and NHL as marginal zone B-cell lymphomas are reported in both disorders and either one is characterized by clonal expansion of IgM RF B cells.

In HCV patients, infection is driven by viral antigen stimulation, and no putative antigen has been discovered in Sjögren's syndrome. Nonetheless, research studies have confirmed RF expression in lymphoma cells of salivary glands with Sjögren's syndrome [36]. Furthermore, Sjögren syndrome is also associated with MC, which is considered as a predictive factor for progression to malignancy in the context of Sjögren syndrome and sometimes also other connective tissue diseases [37]. While available data may not be sufficient to claim a shared pathogenesis of NHL in Sjögren's syndrome and HCV, the role of antigen driven B cells with RF activity is undisputable in the context of MC and lymphoproliferative neoplasms.

CONCLUSIONS

Both HBV and HCV are associated with autoimmune stigmata and the formation of self-antibodies. There is a significant disparity in the frequency of these manifestations induced by hepatitis viruses. Moreover, there is a paucity of studies documenting the interplay of RF with HBV, which precludes a reliable assessment of the proposed differences. However, research on RF in the setting of HCV shows a clear link between seemingly innocuous autoantibody response, autoimmunity, and hematologic neoplasms. The WA cross-idiotype of monoclonal RF in particular needs further investigation for its possible role in predicting these complications. We think that population based studies in the context of high-endemic areas for chronic viral hepatitis may help to determine the connection of RF with HBV and HCV infections, including the risk of developing RA and Sjögren's syndrome and complications such as cryoglobulinemia and lymphoproliferative disorders.

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Capsule

A cellular census of human lungs identifies novel cell states in health and in asthma

Human lungs enable efficient gas exchange and form an interface with the environment, which depends on mucosal immunity for protection against infectious agents. Tightly controlled interactions between structural and immune cells are required to maintain lung homeostasis. **Vieira Braga** et al. used single-cell transcriptomics to chart the cellular landscape of upper and lower airways and lung parenchyma in healthy lungs, and lower airways in asthmatic lungs. The authors reported location-dependent airway epithelial cell states and a novel subset of tissue-resident memory T cells. In the lower airways of patients with asthma, mucous cell hyperplasia is shown to stem from a novel mucous ciliated cell state, as well as goblet cell hyperplasia. The authors reported the presence of pathogenic effector type 2 helper T cells (TH2) in asthmatic lungs and found evidence for type 2 cytokines in maintaining the altered epithelial cell states. Unbiased analysis of cell–cell interactions identifies a shift from airway structural cell communication in healthy lungs to a TH2-dominated interactome in asthmatic lungs.

Nature Med 2019; 25: 1153

Eitan Israeli

Capsule

Effect of disease-modifying anti-rheumatic drugs on bone structure and strength in psoriatic arthritis patients

Simon et al. addressed the question whether the use of methotrexate and biological disease-modifying anti-rheumatic drugs (bDMARDs) impacts bone structure and biomechanical properties in patients with psoriatic arthritis (PsA). This cross-sectional study reviewed PsA patients receiving no DMARDs, methotrexate, or bDMARDs. Volumetric bone mineral densities (vBMDs), microstructural parameters, and biomechanical properties (stiffness/failure load) were determined by high-resolution peripheral quantitative computed tomography and micro-finite element analysis in the respective groups. Bone parameters were compared between PsA patients with no DMARDs and those receiving any DMARDs, methotrexate, or bDMARDs, respectively. The team analyzed 165 PsA patients; 79 received no DMARDs, 86 received DMARDs. Of the DMARDS, 52 were bDMARDs (TNF, IL-17- or IL-12/23 inhibitors) and 34 were methotrexate. Groups were balanced for age, gender, co-morbidities, functional index, and bone-active therapy. Disease duration was longest in the bDMARD group (7.8 ± 7.4 years), followed by the methotrexate group (4.6 ± 7.4), and the no-DMARD group (2.9 ± 5.2). No difference in bone parameters was found between the no-DMARD group and the methotrexate group. In contrast, the bDMARD group revealed significantly higher total (P = 0.001) and trabecular vBMD (P = 0.005) as well as failure load (P = 0.012) and stiffness (P = 0.012). In regression models, age and bDMARDs influenced total vBMD, while age, gender, and bDMARDs influenced failure load and stiffness.

Arthritis Res Ther 2019; 21: 162

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"It is possible to store the mind with a million facts and still be entirely uneducated"

Alec William Bourne (1886–1974), British gynecologist and writer