

Hepatitis B & C and Lymphoma risk

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Infectious Diseases

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10/18/22

Objectives

- 1) Describe the association between Lymphoma and hepatitis C and B.
- 2) Define risk of lymphoma with viral hepatitis C and B and role of viral hepatitis treatment in lymphoma outcomes.
- 3) Outline the proposed pathogenesis of lymphoma in association with viral hepatitis.

Disclosures

- I will not be mentioning any off-label use.
- I have no financial COI to disclose.

Malignancy and Pathogens

The role of certain pathogens in promoting oncogenesis has been well-described throughout the past several decades:

- H. pylori and MALT gastric lymphoma
- HIV and rectal cancer, lung cancer, cervical cancer, lymphoma, Kaposi sarcoma
- HHV-8 and Kaposi sarcoma
- HPV in head/neck, cervical and anorectal cancer
- HBV and hepatocellular carcinoma

HCV and Lymphomagenesis

HCV-induced Carcinogenesis may occur through 3 proposed potential mechanisms:

1. Direct oncogenic effect on cellular proliferation and viability via infection of peripheral blood mononuclear cells. HCV is both lymphotropic and hepatotropic.
 - Acquired point mutations in immunoglobulin and non-immunoglobulin genes
 - Esp. TP53, BCL6, Beta-catenin; increased burden of mutations was noted in patients with lymphoma and HCV, but not in those without HCV
 - Some HCV proteins such as the HCV Protein core and nonstructural protein 5A might direct effect cell proliferation.
 - However, there is no convincing evidence of viral replication in B cells & monocytes.
 - HCV may localize to salivary glands, kidney, skin bone marrow and PBMCs.
 - Viral replication is limited to hepatocytes, for the most part.

Weng & Levy. Hepatitis C Virus (HCV) and Lymphomagenesis. *Leukemia and Lymphoma*. 2002;44(7):1113-1120.

Viswanatha DS, Dogan A. Hepatitis C virus and lymphoma. *J Clin Pathol*. 2007 Dec;60(12):1378-83. doi: 10.1136/jcp.2007.051870. PMID: 18042694; PMCID: PMC2095565.

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HCV and Lymphomagenesis

HCV-induced Carcinogenesis may occur through 3 proposed potential mechanisms:

1. Direct infection of peripheral blood mononuclear cells & direct cellular proliferation via this mechanism.
 - However, there is no convincing evidence of viral replication in B cells & monocytes.
 - Viral replication is limited to hepatocytes
2. Accumulation of genetic events such as BCL-2 rearrangement
 - BCL-2 rearrangements are significantly higher in patients with HCV vs. those without HCV
 - Mixed cryoglobulinemia can convert to overt B-cell lymphoma in some (but not all) patients with HCV.

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3. Indirect transformation via HCV antigen-driven expansion of mono- or oligoclonal B cells > Benign lymphoproliferative disorders *or* frank malignant lymphoma through activated B-cell clones (secondary oncogenic events)

- HCV (E2 viral envelope Ag)-CD81 binding via BCR and stimulation may further promote ongoing cell proliferation.
- CD81 is expressed on most human cells with the exceptions of RBCs and platelets and associate with different proteins in various cell types in the body.
- Mono- and Polyclonal expansion of naïve B cells from persistent CD81 stimulation may occur.
- Monoclonal IgM resolves in patients with HCV who respond to antiviral treatment.
- The LDL receptors in cells are another proposed target for unchecked cell proliferation.

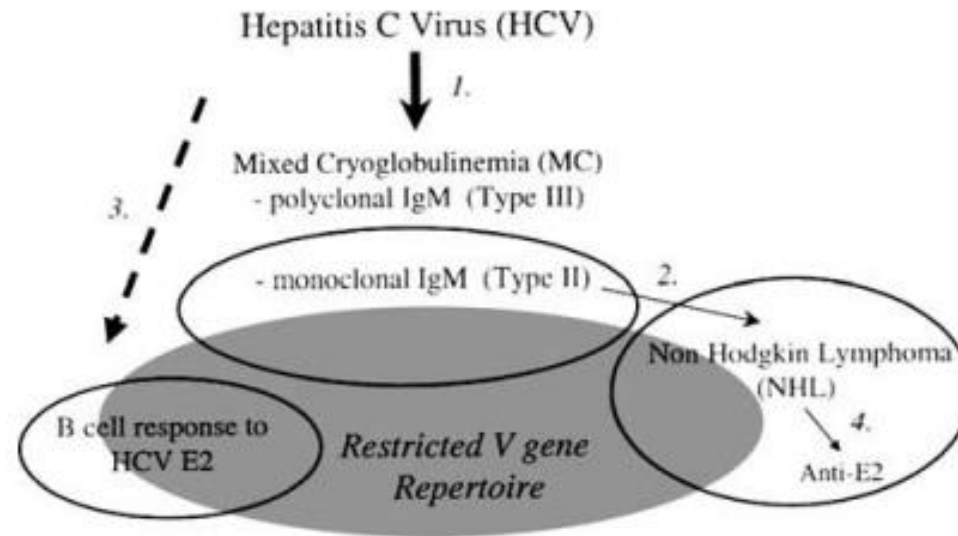


FIGURE 1 Restricted V gene usage is common in HCV-induced B cell responses. (1) A high percentage of patients with mixed cryoglobulinemia are infected with HCV (wide arrow). (2) A low percentage patients with MC progress to NHL (narrow arrow), a progression of a specific B cell clone observed in MC to overt NHL has been documented [53]. The immunoglobulin V region genes expressed in MC and NHL tend to use a restricted and shared repertoire (gray oval). (3) B cell that respond to the envelope protein of the virus, E2, also use this restricted V gene repertoire (dashed arrow). (4) The BCR rescued from one case of NHL was shown to bind HCV E2 [51].

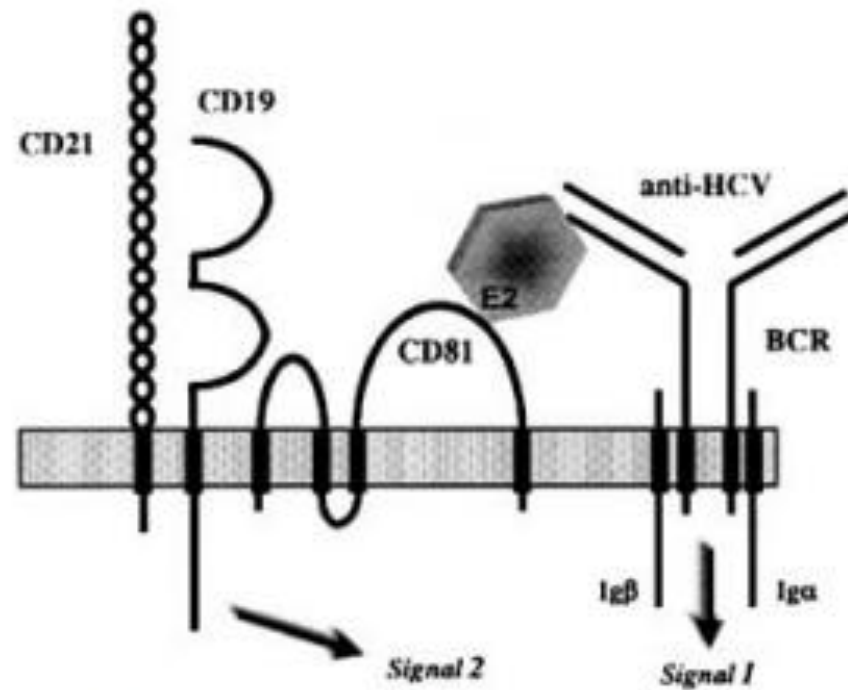


FIGURE 2 Dual signaling model for B cell activation by HCV antigens. B cells that bind HCV antigens through their BCR transmit an activation signal (signal 1) that can be amplified by binding of the viral envelope antigen E2 to CD81 (signal 2). Ig α and Ig β are the signaling components of the BCR complex, CD19 is the signaling molecule in the CD19/CD21/CD81 complex.

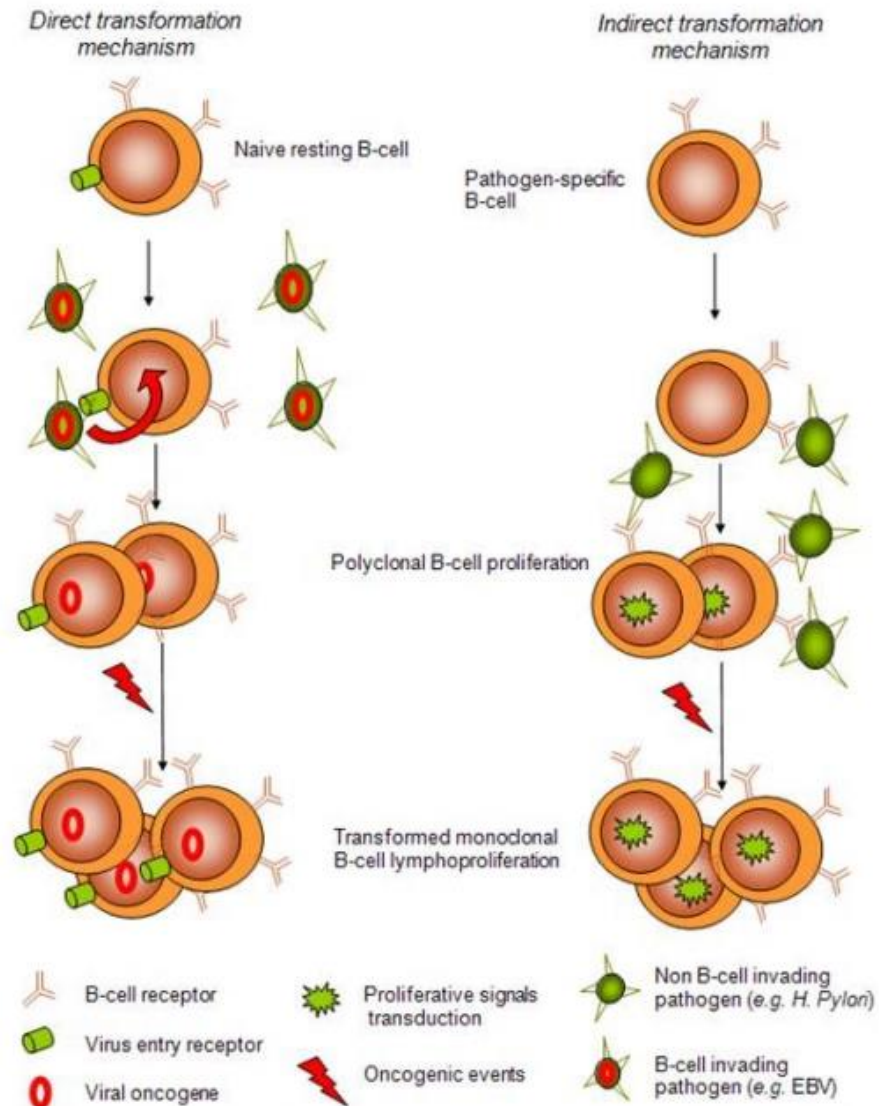


Figure 2. General models of lymphoid transformation by pathogens. Direct transformation model. Infectious agents such as Epstein-Barr virus directly target resting B-cell and establish latent infection. Transcription of viral latent genes with oncogenic potential leads to immortalization of infected B-cell and proliferation, normally kept in check by the immune system of the host. Under certain circumstances (as immune deficiency) or after additional oncogenic mutations, fully transformed EBV-infected B-cell might lead to malignant lymphoma. **Indirect transformation model.** Persisting pathogens such as *Helicobacter Pylori* in chronic infection stimulate antigen-specific B-cell either directly or indirectly through T-cell help. Clonal expansion may develop in responding lymphocytes sometimes ultimately leading to frank lymphoproliferation.

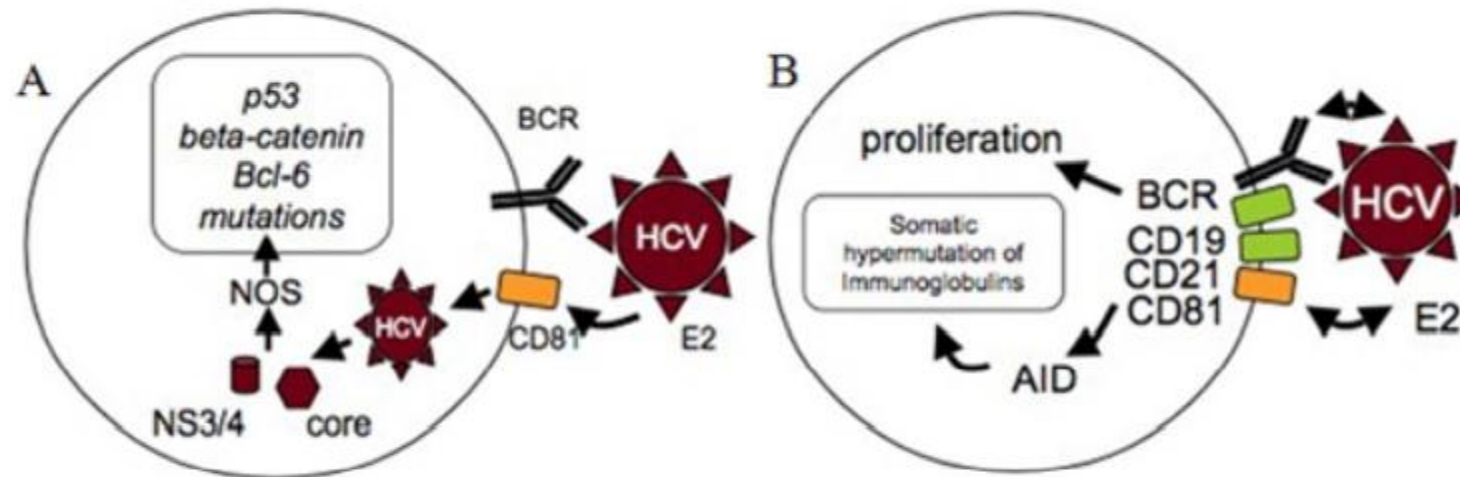


Figure 3. Hypothetical model of B-cell transformation by HCV. 3A. Direct transformation model. Induction of cellular NO-synthase and subsequent mutations of p53, beta-catenin and Bcl-6 by HCV associated core and NS3/4 proteins may participate in B-cell transformation. According to this hypothesis, HCV would directly infect B cells, possibly through CD81-E2 interaction. **3B. Indirect transformation model.** Interaction of E2 and CD81 on the cell surface induces expression of activation-induced deaminase (AID) and somatic hypermutations of immunoglobulin genes and potential proto-oncogenes. This mechanism may participate in B-cell transformation by HCV. B-cell transformation would not need to require direct infection of B-cells by HCV as this interaction takes place between extracellular E2 expressed on the virion and surface CD81.

Mixed cryoglobulinemia (MC)

- 8-10% of patients with mixed cryoglobulinemia develop a lymphoproliferative disorder.
- MC is associated with a 35x increased risk of lymphoma compared to the general population.
- MC is also associated with hepatitis C infection.
 - 50-90% of patients with MC have a positive HCV Antibody.
 - 40-50% of patients with HCV have circulating cryoprecipitate complexes.
 - Antiviral treatment for HCV leads to disappearance of MC in many patients.

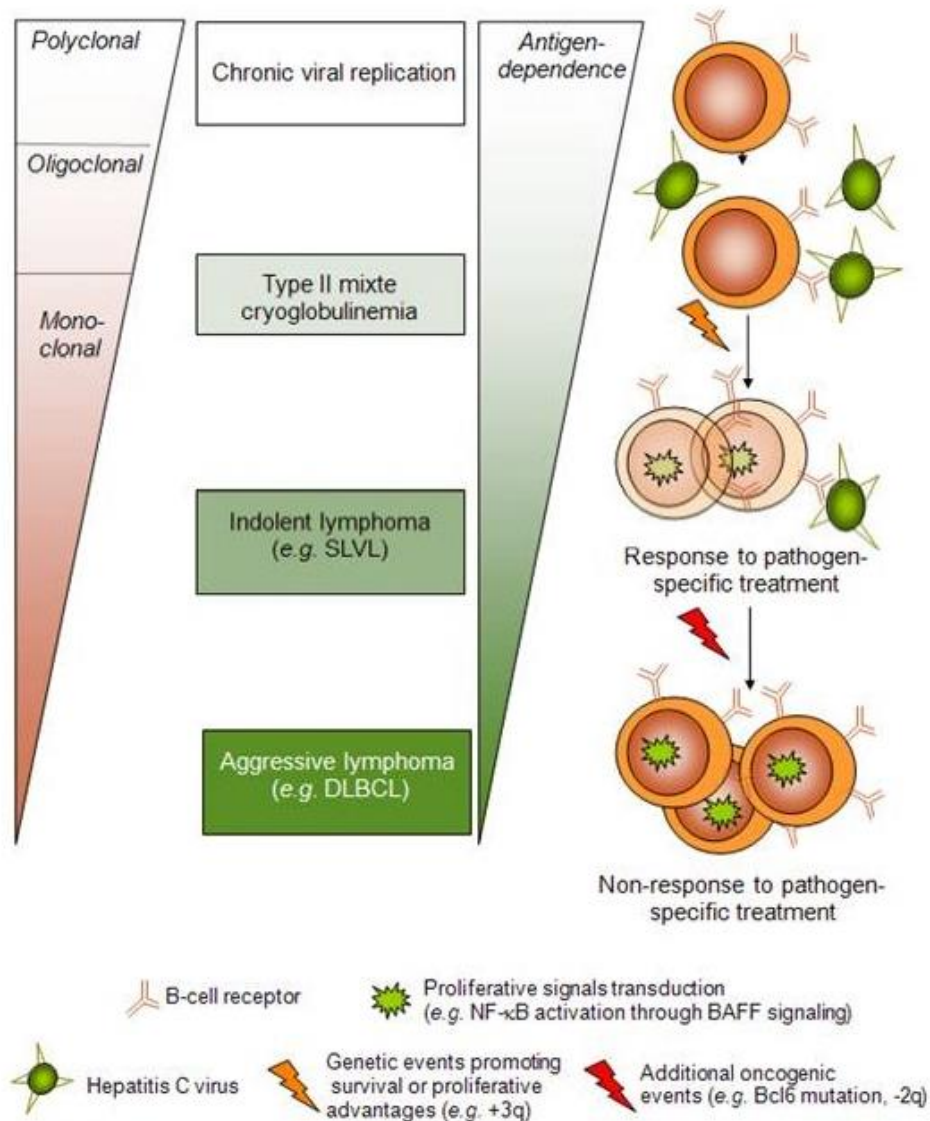


Figure 4. Hypothetical model of progression from mixed cryoglobulinemia to lymphoma. Stimulation of auto-reactive, rheumatoid factor producing and HCV-E2 or NS3 cross-reactive specific B cells might lead to a first-step lymphoproliferative development such as in type II mixed cryoglobulinemia (MC). Pro-inflammatory cytokines, such as BAFF (also called B lymphocyte stimulator, BLyS), a potent stimulator of B-cell survival and proliferation, are thought to play an important role in this mechanism. Eradication of the antigenic source at this stage by interferon with or without ribavirin leads to a decrease of the cryoglobulin load and of the clonal population. Additional oncogenic events may occur in the proliferating cryoglobulin-producing population and lead to transformation into NHL such as marginal zone lymphoma with villous lymphocytes (SLVL). Such transformed B cells would still remain dependent upon antigen stimulation as attested by the regression of the tumor after HCV eradication but without full disappearance of the clonal population. Further oncogenic events, such as 2q loss, may lead to transformation into high-grade lymphoma.

HCV-associated lymphomas & leukemias

- Marginal zone lymphoma
 - Splenic, nodal and extra-nodal
- Small lymphocytic lymphoma/Chronic lymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Diffuse large B-Cell Lymphoma (DLBCL)
- Mantle cell lymphomas
- Primary lymphoma of the liver
- Low-grade MALT lymphomas
- Gastric Lymphoma
- 20-30% increase in NHL among patients w/ HCV

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Bronowicki JP, et al Primary lymphoma of the liver: clinical-pathological features and relationship with HCV infection in French patients. *Hepatology*. 2003 Apr;37(4):781-7.

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Giordano TP, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *JAMA*. 2007 May 9;297(18):

Lymphoma outcomes with HCV

- DLBCL outcomes are worse in patients with HCV.
- NHL outcomes are improved with HCV treatment.
- Lymphoma regression has been documented after anti-HCV therapy.
- Splenic marginal zone lymphoma

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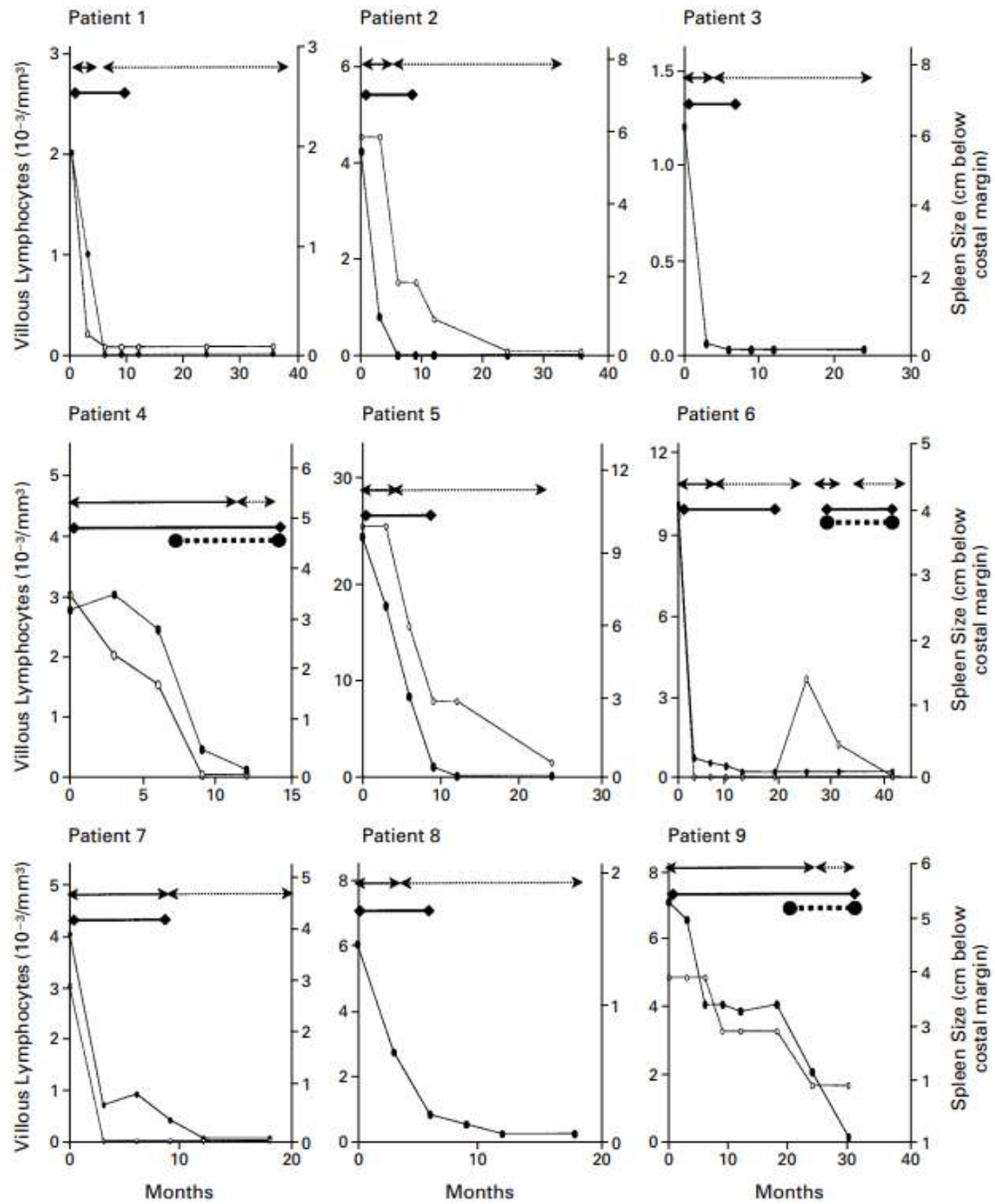
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Hermine et al.

- Nine patients with splenic lymphoma with villous lymphocytes and HCV infection were treated with IFN alfa-2b alone or in combination with ribavirin.
- Six patients without HCV but with splenic lymphoma with villous lymphocytes served as the comparison group.
- In the 9 patients living with HCV and splenic lymphoma, regression of the lymphoma was achieved (in all 9 patients) with treatment of the HCV with IFN and ribavirin.
- Effect has been compared to MALT lymphoma and H. pylori infection/treatment.

- Interferon
- Ribavirin
- Spleen size
- Villous lymphocytes
- Negative HCV RT-PCR
- Positive HCV RT-PCR



Hermine O, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. *N Engl J Med.* 2002 Jul 11;347(2):89-94.

TABLE 2. CHARACTERISTICS OF THE SIX PATIENTS WITH SPLENIC LYMPHOMA WITH VILLOUS LYMPHOCYTES WITHOUT HEPATITIS C VIRUS INFECTION.

| PATIENT NO. | AGE (YR)/SEX | PRIOR THERAPY | SPLEEN SIZE cm below costal margin | ABSOLUTE NEUTROPHIL COUNT | VILLOUS LYMPHOCYTES $\times 10^{-6}/\text{mm}^3$ | PLATELET COUNT | HEMOGLOBIN g/dl | DURATION OF INTERFERON THERAPY mo | OUTCOME AFTER INTERFERON THERAPY |
|-------------|--------------|---------------------------|---------------------------------------|---------------------------|---|----------------|--------------------|--------------------------------------|----------------------------------|
| 10 | 54/F | None | 8 | 1.4 | 4.5 | 88 | 11 | 7 | Treatment failure |
| 11 | 72/F | None | 0 | 2.1 | 44 | 139 | 12 | 9 | Treatment failure |
| 12 | 61/M | None | 10 | 2.3 | 2 | 106 | 10.6 | 6 | Treatment failure |
| 13 | 61/F | Splenectomy, chlorambucil | —* | 1.9 | 94 | 265 | 13 | 6 | Treatment failure |
| 14 | 69/M | None | 10 | 1.1 | 100 | 88 | 10 | 4 | Progression |
| 15 | 58/M | None | 6 | 1.2 | 19 | 89 | 9.8 | 6 | Treatment failure |

*Patient 13 had undergone splenectomy.

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Questions/Comments?