

# Lymphoproliferative disease with mixed cryoglobulinemia and hyperviscosity syndrome in an HIV-infected patient: HCV is the only culprit

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## SUMMARY

The availability of direct antiviral agents (DAAs) offers the possibility to treat HCV-infected patients with a high rate of efficacy and a good safety profile. Little is known about the benefit of DAAs on HCV-related hematological diseases and their complications. We describe the case of an HIV/HCV-infected patient with HCV-related chronic lymphoproliferative disease, mixed cryoglobulinemia and hyperviscosity syndrome. Treatment with direct antiviral agents (DAAs) cured HCV infection and its complications, while HCV re-infection caused recrudescence of the associated diseases.

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## INTRODUCTION

According to the most recent estimates, about 170 million people in the world have chronic hepatitis C virus (HCV) infection. HCV is a leading cause of liver-related mortality with 350,000 deaths/year (Zaltron *et al.*, 2012). The development of direct-acting antiviral agents (DAAs) has offered a new effective therapeutic option for patients (Zopf *et al.*, 2016). In Italy, access to therapy with these drugs is not universal, but limited to categories of patients defined by the Italian Drug Agency (AIFA). According to AIFA (3<sup>rd</sup> criterion), B-cell lymphoproliferative disorders and cryoglobulinemic syndrome with organ damage are eligibility criteria for treatment with new drugs. HCV infection is known to be a trigger to B-cell proliferation that can lead to autoimmune and neoplastic disorders such as mixed cryoglobulinemia and/or B-cell non-Hodgkin lymphoma (NHL) (Voma *et al.*, 2016; Dammacco *et al.*, 2000). The mechanisms whereby HCV establishes these complications are still poorly understood but much evidence suggests that the immunogenetic profile may play an important role (De Re *et al.*, 2016). People with chronic HCV infection have a 2.5-fold increase in the risk of developing NHL (Pozzato *et al.*, 2016). Mixed type II cryoglobulinemia represents the most investigated HCV-related extrahepatic disorder. It is a systemic vasculitis involving small-to-medium vessels due to circulating cryoglobulins (CG) containing both rheumatoid factor IgM and polyclonal IgG. Hyperviscosity syndrome is often associated with CG due

to hematological malignancies and may require treatment with plasma exchange. Regression of B-cell lymphoproliferative disorders after interferon-based treatment is the main supportive evidence of an etiological link with HCV infection. Few data on the favorable effect of DAAs on the course of these diseases have been reported so far (Arcaini *et al.*, 2016; Peveling-Oberhag *et al.*, 2016, Merli *et al.*, 2016). We describe an emblematic case of an HIV-coinfected patient with chronic lymphoproliferative disorder complicated by cryoglobulinemia and hyperviscosity syndrome which regressed completely under DAAs and presented again after HCV reinfection with a different genotype.

## CASE REPORT

A 45-year-old man with HIV/HCV (4a/4c/4d genotype defined in 2010) co-infection was admitted to the General Medicine ward of the Spedali Civili general Hospital in Brescia (Italy) on October 15, 2015 for abdominal pain. He was a homeless person referring intravenous drug use (IVDU) and poor compliance with antiretroviral therapy (atazanavir/ritonavir and tenofovir/emtricitabine). Abdomen CT scan supported the diagnosis of non-specific colitis and antimicrobial therapy with ampicillin/sulbactam and metronidazole was started. On October 19, 2015 the patient presented a syncopal episode: brain CT scan showed only chronic post-traumatic injuries. On November 1, the patient presented a further syncopal episode followed by respiratory arrest requiring orotracheal intubation and he was transferred to the Intensive Care Unit. Brain CT scan was unchanged. He underwent mechanical invasive ventilation until November 14, with various concomitant diagnoses (*Bacillus sp* sepsis, left pneumonia and critical illness myopathy/neuropathy). Blood tests showed hyperviscosity (8 cP, nv 1.6-2.2 cP) and circulating

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monoclonal IgM. Bone marrow biopsy was performed, excluding lymphoma. However, lymphocyte typing showed chronic lymphoproliferative disease (CD5-, CD20+). Glucocorticoid therapy was started and the patient underwent plasma exchange on November, 12, 13 and 16. On November 24, he was transferred to our Department of Infectious Diseases. Further plasma exchanges were needed in December, January and February, 2016. On January 15, DAAs anti-HCV treatment with ombitasvir+paritaprevir+ritonavir+ribavirin was started, according to HCV genotype and AIFA guidelines. On April 1, the patient was transferred to a Rehabilitation Institute, where he completed DAAs treatment on April 8. At discharge, viscosity was 4 cP, hematocrit (Ht) 36% and HCV RNA was <15 UI/mL. One month after the end of treatment, viscosity was 2.6 cP, cryocrit 21.6%, Ht 36.4% and HCV RNA persisted negative. Notwithstanding repeated counseling, the patient did not attend the scheduled visits and presented on September 28, referring IDVU in the last few months. Blood tests were repeated, showing HCV re-infection (HCV genotype 3a, HCV RNA 63,320 UI/mL) and hyperviscosity (8.6 cP), with high cryocrit 46%. In the following weeks the patient was therefore admitted to hospital where multiple plasma exchanges were performed to control the hyperviscosity syndrome. Lymphocyte typing identified a recrudescence of the previously diagnosed chronic lymphoproliferative disease (CD5-, CD20+). Elastography performed on December 16 showed a stiffness of 5.2 kPa (F1 stage of fibrosis) and a new 12-week cycle of antiviral therapy with sofosbuvir and daclatasvir was started on December 15, according to the AIFA criterion (n. 3). HCV RNA was <15 UI/mL at week 4 and viscosity was reduced (4.7 cP). Virological response was also demonstrated 4 weeks after treatment.

## DISCUSSION

In the reported case, our patient presented HCV-related chronic lymphoproliferative disease, mixed cryoglobulinemia and hyperviscosity syndrome. Treatment with DAAs cured HCV infection and concomitant diseases, while HCV re-infection determined a new onset of mixed cryoglobulinemia with hyperviscosity syndrome. Even though the first genotype was defined in 2010 and the patient was lost to follow-up and therefore we could not demonstrate

the sustained virological response (SVR) at 12 weeks after treatment, referred risk factors along with the different genotype found, allow us to attribute the new HCV infection to re-infection. This event was strictly associated with recrudescence of the previous complications, strongly suggesting the causal role of HCV infection. Our case is in line with the recent literature (Pozzato *et al.*, 2016, Arcaini *et al.*, 2016; Peveling-Oberhag *et al.*, 2016), showing that the high rate of SVR achieved with the new DAAs could offer the opportunity to break the etiological link between HCV and B-cell lymphoproliferative disorders inducing their regression. Current guidelines do not allow access to the new DAAs for every HCV-infected patient, the reported case raises ethical issues about the decision to repeat treatment in patients who failed a previous therapy due to persisting behavioral risk factors for HCV infection. Considering the benefit the hematological disease would have had and respecting the AIFA criteria, we restarted the therapy, counseling our patient about prevention and providing support in a rehabilitation center.

## References

- Arcaini L., Besson C., Frigeni M., Fontaine H., Goldaniga M., et al. (2016). Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. *Blood*. **128**, 2527-2253.
- Dammacco F., Sansonno D., Piccoli C., Racanelli V., D'Amore F.P., et al. (2000). The lymphoid system in hepatitis C virus infection: autoimmunity, mixed cryoglobulinemia, and Overt B-cell malignancy. *Semin Liver Dis.* **20**, 143-157.
- De Re V., De Zorzi M., Caggiari L., Lauletta G., Tornesello M.L., et al. (2016). HCV-related liver and lymphoproliferative diseases: association with polymorphisms of IL28B and TLR2. *Oncotarget*. **7**, 37487-37497.
- Merli M., Carli G., Arcaini L., Visco C. (2016). Antiviral therapy of hepatitis C as curative treatment of indolent B-cell lymphoma. *World J Gastroenterol*. **22**, 8447-8458.
- Peveling-Oberhag J., Arcaini L., Bankov K., Zeuzem S., Herrmann E. (2016). The anti-lymphoma activity of antiviral therapy in HCV-associated B-cell non-Hodgkin lymphomas: a meta-analysis. *J Viral Hepat.* **23**, 536-544.
- Pozzato G., Mazzaro C., Dal Maso L., Mauro E., Zorat F., et al. (2016). Hepatitis C virus and non-Hodgkin's lymphomas: Meta-analysis of epidemiology data and therapy options. *World J Hepatol*. **8**, 107-116.
- Voma C.B., Levinson S.S. (2016). Analysis, detection and quantitation of mixed cryoglobulins in HCV infection: brief review and case examples. *Clin Chem Lab Med*. **54**, 1853-1859.
- Zaltron S., Spinetti A., Biasi L., Baiguera C., Castelli F. (2012). Chronic HCV infection: epidemiological and clinical relevance. *BMC Infect Dis.* **12** (Suppl. 2), S2.
- Zopf S., Kremer A.E., Neurath M.F., Siebler J. (2016). Advances in hepatitis C therapy: what is the current state-what come's next? *World J Hepatol*. **8**, 139-147.