OCTOBER 11-12, 2024 MILAN, ITALY
DeltaCure 3rd International Meeting
P42
Poster for you

HIV-HBV-HDV co-infection. Case presentation.

MN Radu[1], C Tudoran[1], RB Băloi[1], FA Căruntu[1, 2]

1. *National Institute for Infectious Diseases "Prof. Dr. Matei Bals", Bucharest, Romania*
2. *University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania*

Introduction

- According to UNAIDS (The United Nations Program on HIV and AIDS), there are 39 million people infected with HIV worldwide, of which 29.8 million are receiving antiretroviral treatment. The aim is to reach the global target of 35 million people receiving treatment by 2025.
- According to data presented by the Department for Monitoring and Evaluation of HIV/AIDS Infection in Romania from The National Institute for Infectious Diseases "Prof. Dr. Matei Bals" (INBIMB), the situation in Romania is as follows[1]:
  - The main routes of transmission in new cases were unprotected heterosexual sex (60%), MSM (31%) and intravenous drug use (7%).
  - June 30, 2023: The number of HIV/AIDS patients was 18,015, of which 147 were in the age group 0-14 years, 129 in the age group 15-19 years and 17,739 in the age group ≥ 20 years.
  - Total HIV/AIDS cases (cumulative 1985-2023) was 27,465, of which: total HIV cases (cumulative 1992-2023) was 9,280, total AIDS cases (cumulative 1985-2023) was 18,185, total AIDS deaths from 1985-2023 was 8,472.
- HDV infection in Romania seems to account for 23.4% of HBV patients, approximately 200,000 people[2].
- We have no statistics on HIV-HBV-HDV co-infected patients in Romania. However, our medical practice recommends testing HBsAg-positive patients for HIV and HDV.

Case presentation

- We would like to present the case of a 34-year-old man diagnosed in 2023 in his hometown with HIV infection (immunologic stage C3) and HBV/HDV-associated liver cirrhosis. The patient received antiretroviral therapy (Dolutegravir/Lamivudine), with virologic response but no immunologic improvement. He was referred to INBIMB for further investigations and therapeutic options.
- We took over the patient in March 2024. The patient appears cachectic, pale, with alopecic areas on the scalp, vulgar warts on the upper limbs, giant genital condylomatosis, and inguinal and axillary lymphadenopathies.
- During hospitalization, the patient was evaluated clinically, biologically, and through imaging, with the following findings:
  - Biological at admission: HBsAg-positive, HBeAg-negative, HDV-Ac-positive, HIV-RNA undetectable, HBV-DNA undetectable, HDV-RNA aprox. 6 log10 IU/ml.
  - Upper GI endoscopy: Portal hypertension syndrome with medium esophageal varices in the lower 1/3.
  - Cardiac ultrasound: normal.
  - Ophthalmologic evaluation: normal.
  - Pelvic CT scan: Partially necrotic lymphadenopathies (right obturator 38 mm, bilateral inguinal maximum 53 mm left).
  - Cervical and thoracic CT scan: no signs of metastasis or other suspected diagnoses.
  - Abdominal MRI with hepatobiliary contrast agent: cirrhotic liver without tumor-like lesions, no signs of thrombosis in the portal venous axis (PV=13 mm, SMV=12 mm, retropancreatic SV=12 mm), splenomegaly (19/5.9/17.17 cm).
  - Lymph node biopsy: lymph node metastasis from moderately differentiated squamous cell carcinoma (G2), HPV-associated; lymph node tuberculosis and Mycobacterium avium complex infection were excluded.
- These findings outline the following diagnoses:
  - HIV infection (AIDS stage).
  - HBV/HDV-associated liver cirrhosis (Child-Pugh score=7 points, MELD-Na score=13 points).
  - Portal hypertension with hematologic hypersplenism and esophageal varices.
  - Scrotal squamous cell carcinoma with locoregional lymph node metastases.
- The patient received antiretroviral therapy (Bictegravir/Emtricitabine/Tenofovir), prophylactic treatment for opportunistic infections (Trimethoprim/Sulfamethoxazole, Clarithromycin), and non-selective beta-blockers. The choice of antiretroviral treatment was made considering hepatic dysfunction, viral hepatitis, concomitant medications and the prospect of oncologic treatment.
- The patient was referred to the oncology department for the management of the carcinoma, and radiotherapy was performed on the scrotal tumor formation.

Results

- Our patient's evolution from March 2024 to present, is detailed in **Table 1**.

Table 1 **PATIENTS EVOLUTION**

	MARCH	APRIL	JULY	AUGUST
LYMPHOCYTE COUNT (*10³/ µL)	0.3	0.1	0.1	0.23
CD4 COUNT	18	35	17	-
CD8 COUNT	144	232	30	-
HEMOGLOBIN (g/dL)	8.9	11.3	7.9	8.5
PLATELET COUNT (*10³/µL)	73	80	49	78
D-DIMER (µg/mL)	-	-	2.94	1.47
INR	1.52	1.56	1.47	-
AST (U/L)*	103	88	96	46
ALT (U/L)*	81	49	57	24
GGT (U/L)	85	98	42	41
BILIRUBIN (mg/dL)	1.3	1.4	2.6	1.66
ALBUMIN (g/dL)	2.6	1.8	-	-
GAMMA (g/dL)	2.25	-	-	-

*AST ULN(upper limit of normal)=17-59 U/L; ALT ULN=4-50 U/L

- On CT scan re-evaluation after radiotherapy in July 2024, thrombosis of the superior mesenteric vein (VMS) and of the portal vein (VP), as well as ascites, were detected. The patient received antithrombotic therapy (Fondaparinux, taking into account thrombocytopenia) and diuretics, with favorable evolution.
- The patient was referred to an oncology specialist, where immunotherapy with Cemiplimab (which enhances T lymphocyte response, including anti-tumor activity, by blocking PD-1 binding to the PD-L1 and PD-L2 ligands) was initiated and was well tolerated.

Discussion

- Immunological mechanisms in HIV infection are now better understood: destruction of lymphoid tissue architecture, action on LyT CD4+, LyB hyper-reactivity, behavior on Mo-Ma as an important factor for viral reservoir formation, Ag-presenting cells (APCs). Regarding hepatitis D virus (HDV) infection, we are gaining insights into both the pathophysiology and the virus-host interactions. This knowledge helps us in staging HIV infection, considering both viral control and the vulnerability caused by the immunosuppression. From the virological standpoint, our patient has shown favorable progress, with HIV-RNA remaining below the detection limit. However, immunological improvement has yet to be achieved.
- What we know about CD4 T cells[3], [4], [5]:
  - CD4 T cells are involved in acquired immunity.
  - naïve CD4 T cells are found freely in the bloodstream, and, by expressing specific co-receptors, can be localized in lymph nodes and spleen.
- The liver's architecture allows interaction between circulating CD4 T cells and APCs in the sinusoids. The interaction between circulating CD4 T cells and APCs in the sinusoids not only makes the liver a site for receiving naïve T cells, but also contributes to their differentiation into effector cells[3].
- Impact of HIV on CD4 T cells [4], [5]:
  - direct effects: HIV infects CD4 T cells, causes cytotoxicity and reduces their absolute number.
  - indirect effects: HIV decreases the proliferation and differentiation of CD4 T cells, reduces colony formation and lowers the expression of CD28 receptor on CD4 T cells (a crucial co-stimulatory receptor for normal T cell activity).
  - the combined result is a decrease in CD4 T cell counts and immunosuppression.
- Impact of liver dysfunction on CD4 T cells[6], [7]:
  - portal hypertension leads to congestive splenomegaly and CD4 T cell splenic sequestration.
  - it is plausible that advanced fibrosis and portal hypertension lead to T cell sequestration, causing low CD4 T cell counts, given the liver's known effects on blood cell lines.
  - whether CD4 T cell depletion occurs only in advanced fibrosis or also in earlier stages of liver disease is still unclear.
- Questions arising from our patient's case may be related to the pathophysiology of the interaction between HIV infection and liver disease[6], [7]:
  - was the progression of liver disease more likely due to HIV-HBV-HDV co-infection and low CD4 T cell counts?
  - did immunosuppression itself contribute to the progression of the liver disease?
  - is a low CD4 T cell count associated with a higher risk of liver-related events, as seen with the patient's PV and SMV thrombosis?
  - does the reduced CD4 T cell count increase the risk of malignancy, given their role in antitumor response?
  - is the persistent low CD4 T cell count for this patient due to HIV infection (despite undetectable HIV-RNA under antiretroviral therapy) or liver cirrhosis and uncontrolled HDV infection?
  - can HIV infection be considered controlled given the undetectable viremia?
  - can we accurately stage the patient's immunodeficiency if the exact cause of the low CD4 T cell count remains unclear?
  - given the concurrent low CD8 T cell count, is the immunosuppression more likely caused by the liver disease?
  - can immunologic therapy (e.g., Cemiplimab) initiated for scrotal carcinoma enhance the hepatic immune response against HBV and HDV through blocking of inhibitory receptors (CTLA4, PD-1, PD-L1)?
  - should we anticipate immune reconstitution inflammatory syndrome at this patient, and if so, how should we manage an exacerbation in the setting of HDV infection?
- At this stage in our patient's case, the main challenge lies in managing HDV infection and liver disease. The patient is receiving antiretroviral therapy according to current guidelines and oncological treatment for carcinoma. However, we remain vulnerable in terms of antiviral control for HDV and complications related to liver disease.

Conclusion

- An estimated prevalence of HIV-HBV-HDV co-infection in Romania is not currently available.
- All HBsAg-positive patients should be tested for HDV and HIV. Early diagnosis could offer a therapeutic opportunity for patients with HIV-HBV-HDV co-infection.
- Understanding the immunological impact and viral interactions in HIV-HBV-HDV coinfection is critical for physicians managing such patients, given the severity of the co-infection, complexity of treatment, and need for a multidisciplinary approach.
- At this time, therapeutic solutions for our young patient do not provide full control over all diagnoses.

Reference

1. National Institute for Public Health of Romania, Dec 2023 - https://insp.gov.ro/
2. Gheorghe L, Csiki IE, Iacob S,et al. J Gastrointestin Liver Dis 2015; 24: 413-422
3. Functional heterogeneity of CD4+ T cells in liver inflammation. Franziska Muscat1,2, Anna Woestemeier1, Nicola Gagliani1,2,3. Published online: 31 August 2021 (Springer)
4. Immune Control of HIV. Muthukumar Balasubramaniam, Jui Pandhare, Chandravanu Dash. HHS Public Access Published in final edited form as: J Life Sci (Westlake Village). 2019 June ; 1(1): 4–37.
5. CD28 costimulation and CD28 expression in T lymphocyte subsets in HIV-1 infection with and without progression to AIDS. H. Choremi-Papadopoulou, N. Panagiotou, E. Samouilidou, F. Kontopidou, V. Viglis. Clin Exp Immunol 2000; 119:499±506
6. Persistently low CD4 cell counts are associated with hepatic events in HCV/HIV coinfected patients: data from the national free antiretroviral treatment program of China Weiyin Lin, Huolin Zhong, Chunyan Wen, Yaozu He, Xiaowen Zheng, Hong Li, Xiejie Chen, Haolan He, Jinfeng Chen, Lijuan Chen, Cong Liu, Xiaoping Tang, Weiping Cai, Linghua Li Chinese Medical Journal 2022;135(22) www.cmj.org
7. The Implications of LowAbsolute CD4 Counts in Patients With Cirrhosis and Human Immunodeficiency Virus. Open Forum Infectious Diseases; Timothy Sullivan Division of infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, New York