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Poster for you

Hepatitis delta virus (HDV) replication through HBV integrants in HCC recurrence after liver transplantation

L. Di Marco[1,2], N. De Maria[3], A. Pivetti[3], A. Colecchia[3], A. Romanzi[3], A. Spallanzani[1], G. Guaraldi[4], G. Dolci[4], G. Ciusa[5], F. Di Benedetto[6], P. Magistri[6], S. Di Sandro[6], E. Degasperi[7], M.P. Anolli[7], P. Lampertico[7], D. Giosa[8], D. Lombardo[9], G. Raimondo[9], T. Pollicino[9]

1. Department of Oncology and Hematology, Oncology Unit, University Hospital of Modena and Reggio Emilia, University of Modena and Reggio Emilia, Modena, 41124, Italy.
2. Clinical and Experimental Medicine Program, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, 41125 Modena, Italy
3. Chimomo Department, Gastroenterology Unit, University Hospital of Modena and Reggio Emilia, University of Modena and Reggio Emilia, 41124 Modena, Italy
4. Department of Infectious Diseases, University Hospital of Modena and Reggio Emilia, University of Modena and Reggio Emilia, Modena, 41124, Italy
5. Infectious Diseases Unit, ARNAS "Civico-Di Cristina-Benfratelli", Palermo, Italy.
6. Hepato-pancreato-biliary Surgery and Liver Transplantation Unit, University of Modena and Reggio Emilia, Modena, 41124, Italy
7. Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
8. Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy.
9. Department of Clinical and Experimental Medicine, University Hospital of Messina, Messina, Italy

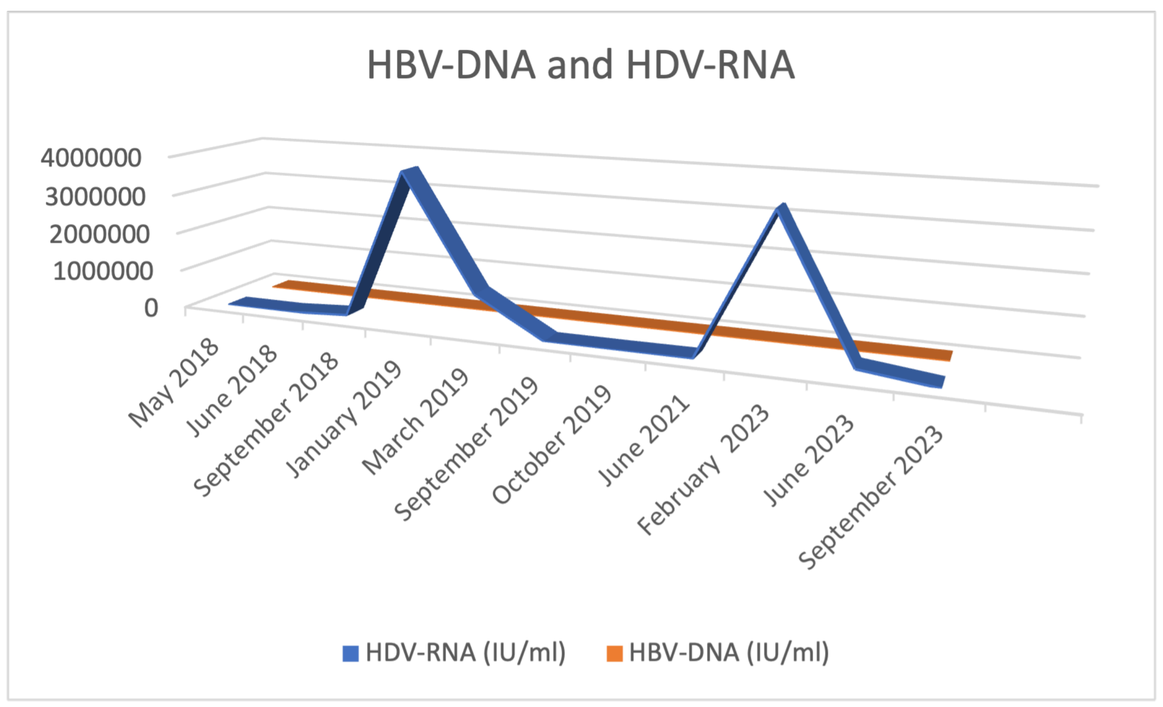
Introduction

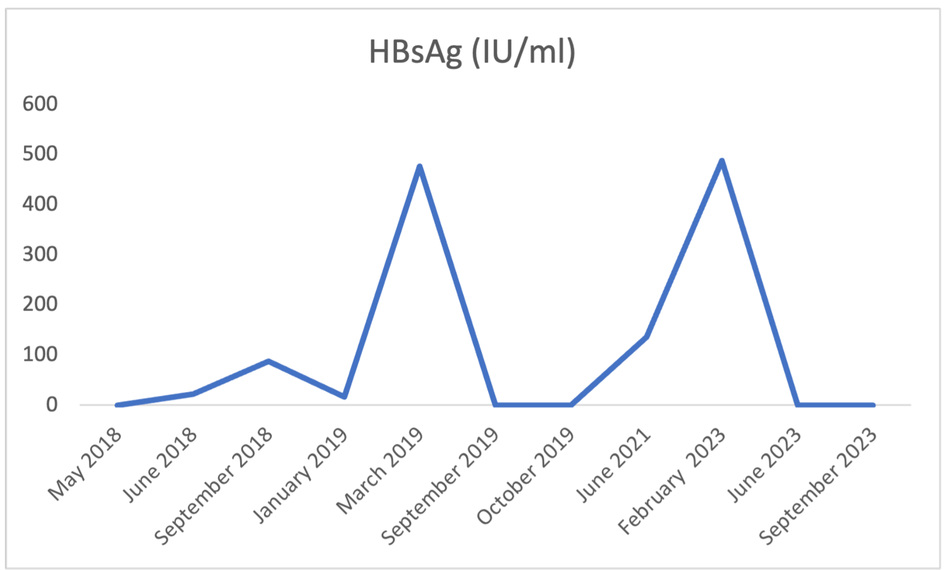
Hepatitis D Virus (HDV) is a unique defective RNA virus that requires the helper function of HBV for viral assembly and in vivo transmission. It is a highly pathogenic virus that causes the least common but most severe and rapidly progressive form of chronic viral hepatitis, leading to cirrhosis in about 80% of the cases within 10 years. HDV-related cirrhosis may be a stable disease for many years, but a high proportion of patients eventually die of hepatic decompensation or hepatocellular carcinoma (HCC) unless they undergo liver transplantation (LT)

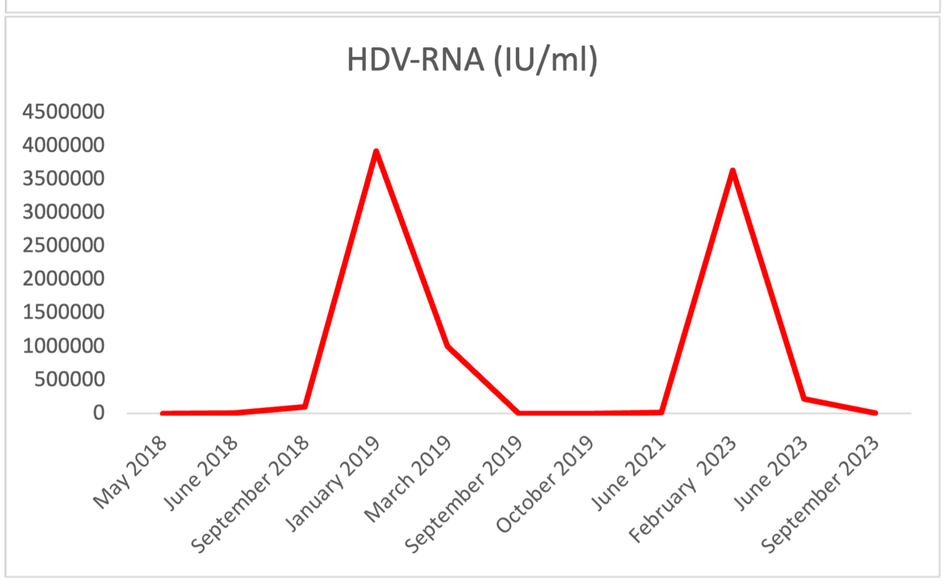
Case Report

- **In 2012**, a 52-year-old man with a history of injection drug use and co-infections with hepatitis C (HCV), B (HBV), D (HDV), and HIV underwent a liver transplant (LT) for hepatocellular carcinoma (HCC).
  Following LT, Tacrolimus, Bictegravir/Emtricitabine/TAF, anti-HBs immunoglobulins, and anti-HCV therapy were initiated. HBsAg, HBV-DNA, HDV-RNA, and HCV-RNA became negative.
  Molecular analyses of the HCC tissue revealed high levels of HDV-RNA (88,400 copies/cell), low levels of total HBV-DNA (0.00001 copies/cell), and HBV cccDNA (0.00008 copies/cell), with no detectable HBV-RNA. High-throughput HBV integration sequencing (HBIS) identified 657 HBV integration sites. HBV integrants primarily included HBx gene sequence.

- **In 2018,** HBsAg reversion was observed with HDV-RNA >19,000 copies/mL, while HBV-DNA remained undetectable.
- **In 2019,** HDV-related hepatitis occurred. HDV-RNA concentrations were elevated at intrahepatic level (3,920,000 copies/cell), and low in the serum (214 IU/mL). Intrahepatic HBcAg, HBsAg, HBV DNA, HBV cccDNA, and HBV-RNA were undetectable.
  A CT scan showed an isolated HCC recurrence in the left adrenal gland, confirmed by histology after adrenalectomy.
  Real-time PCR revealed high levels of HDV-RNA (5.5 copies/cell), low levels of total HBV-DNA and HBV cccDNA (0.00009 and 0.00001 copies/cells, respectively), and undetectable HBV-RNA in adrenal gland tissue. HBIS identified 3497 HBV integrations, most of which included HBs gene sequences. After adrenalectomy, serum HBsAg and HDV-RNA became undetectable. Anti-HBs immunoglobulins and Everolimus were continued.
- **In 2021,** the patient became HBsAg positive again. CT scan showed two HCC nodules in the liver and one in the right adrenal gland. TACE was performed, and therapy with Sorafenib was started.
- **In February 2023,** a further episode of HDV hepatitis occurred. Serum levels of HDV-RNA and HBV-DNA were 3,631,360 IU/ml and <10 IU/ml, respectively. There was no radiological evidence of hepatic neoplastic lesions. Radiofrequency ablation (RFA) on the right adrenal gland was performed, systemic therapy was switched to regorafenib and Bulevirtide was started.
- **In June 2023,** HDV-RNA serum levels declined (48,638 IU/ml), and transaminase values were within the normal range.







CONCLUSIONS

This case shows that:

- HDV may replicate in extrahepatic metastases of HCC, as confirmed by the decrease of HDV-RNA levels after RFA and BLV therapy
- HBV integration in HCC metastases can lead to the production of HBsAg.
- HBsAg production from integrated HBV-DNA in absence of HBV replication may result in HDV propagation even from HCC metastatic lesions.