IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 12 Ser.6 (December. 2023), PP 50-53
www.iosrjournals.org

A Case Of Primary Biliary Cholangitis And Associated Cmv Infection In An Immunocompetent Adult

M. Kadiri,I. Benelbarhdadi, M. Borahma, Fz. Ajana.
Department Of Hepato-Gastroenterology C, Ibn Sina Hospital, Mohamed V University, Rabat-Morocco

Abstract:
A 58 years old female patient was admitted in our hospital with a diabetic ketoacidosis, severe jaundice, fever and elevated liver function tests with acute cytolysis and cholestasis. Based on clinical and laboratory features, a complete etiological workup has been performed (viral hepatitis tests, liver atoimmune tests, liver biopsy..) and showed a positive anti-sp100 antibodies with a level of 45,1 U (Normal>25) , with histological signs of lymphocytic destructive cholangitis with cirrhosis on liver biopsy making the diagnosis of biliary primary cholangitis
Given the autoimmun context disease and the acute hepatitis, a pantropic viruses assessment has been requested (Herpes simplex virus, Cytomegalovirus, and Epstein-Barr virus) showing a high titers of serum globulin positive IgG and IgM for CMV with a high viral load (5483 UI/mL).The HIV serological tests and serum levels of immunoglobulins (IgG,IgA, IgM) were negative, a research for severe disease related to cmv infection was done, including colitis, pneumonitis, retinis and encephalitis and were all negative.
according to the significant viral load, a treatment with ganciclovir was initiated,The patient responded well to therapy. unfortunately due to the end-stage of her liver disease, the patient died after 3 months of diagnosis.
this case could suggest a link between cmv infection and primary biliary cirrhosis.

Keywords: *Cytomegalovirus infection; primary biliary cholangitis, immunocompetent adult, cirrhosis*

Date of Submission: 15-12-2023 Date of Acceptance: 25-12-2023

I. Introduction:

Primary biliary cholangitis (PBC) is an autoimmune cholestatic disease that mainly affects women with an F/M ratio of 9 to 10. It is characterized by inflammation and destruction of small bile ducts due to lymphocytic infiltration resulting in intrahepatic cholestasis and hepato-cellular failure. The exact pathogenesis of this reaction is still unknown, but it is likely related to genetics, immunological and environmental factors, including viral infections such as CMV, which can either complicate or reveal the disease.

CMV infection is a common viral infection that can cause severe disease in immunocompromised patients such as those with HIV or undergoing chemotherapy or organ transplantation but it is exceptionally seen in immunocompetent individuals. While CMV infection is not typically associated with PBC in immunocompetent adults, there have been rare cases documented in the literature and to our knowledge , our case represents only the second one to be reported.

The aim of our study is to investigate the cause-and-effect relationship between CMV infection and seropositive PBC by describing the clinical and paraclinical characteristics of this patient ;is this a triggering factor or a simple association?

II. Case presentation:

A 58-year-old moroccan female was admitted in our hospital for investigation of liver dysfunction test, she had a history of type II diabetes treated with insulin for 18 years and a positive microscopy pulmonary tuberculosis treated for 6 months. She had no history of hepatotoxic medication, alcohol or drug use.

She was initially hospitalized for the management of diabetic ketoacidosis and progressive cholestatic jaundice with increasing abdominal volume, fever and asthenia. Physical examination revealed a stable patient, jaundiced, grade II ascites and pruritis without hepatic encephalopathy .

An abdominal-pelvic ultrasound was performed, revealing an heterogeneous liver with signs of portal hypertension and ascites without bile duct dilation.

Biological tests revealed abnormal liver functions with very high levels of cytolysis and cholestasis as well as liver dysfunction biomarkers (prolonged PT/INR as well as decreasing factor V activity and increasing total bilirubin)

	At diagnosis	Normal range
Total bilirubin	290	2-12 mg/l
Direct bilirubin	183	0-5 mg/l
Asparate aminotransferase (ASAT)	524	5-34 Ui/l
Alanine aminotransferase (ALAT)	475	0-55 Ui/l
γ-glutamyl transpeptidase (GGT)	437	11-59 Ui/l
Alcaline phosphatase (PAL)	632	40-150 Ui/l
Albumin	23,4	35-52 g/l
Prothrombin time and internation normalized ratio (INR)	38% 2,13	70-100% 0.8-1,2
Hemoglobin	13	12-15 g/dl
White blood cells	3340	4000-10000/ul
Platelets	118000	150000-400000 /ul
Creatinine	9	7,2-12,5 mg/l

Figure 1 : Laboratory Data

Etiological assessment was the following:
Nominal viral serological tests were negative (HAV, HBV, HCV, HEV)

Liver autoimmun tests was negative for fluorescence antinuclear antibody, antismooth muscle antibodies (ASM) , Liver kidney microsomal type 1 antibody (anti-LKM1) and Anti-mitochondria M2 antibody, but was positive to antinuclear antibody(ANA) (enzyme-linked immunosorbent assay) (>1/80) and to anti-sp100 antibodies (45.1U/ml), with histological signs of lymphocytic destructive cholangitis with massive lobular necrosis cirrhosis F4 making the diagnosis of primary biliary cholangitis.

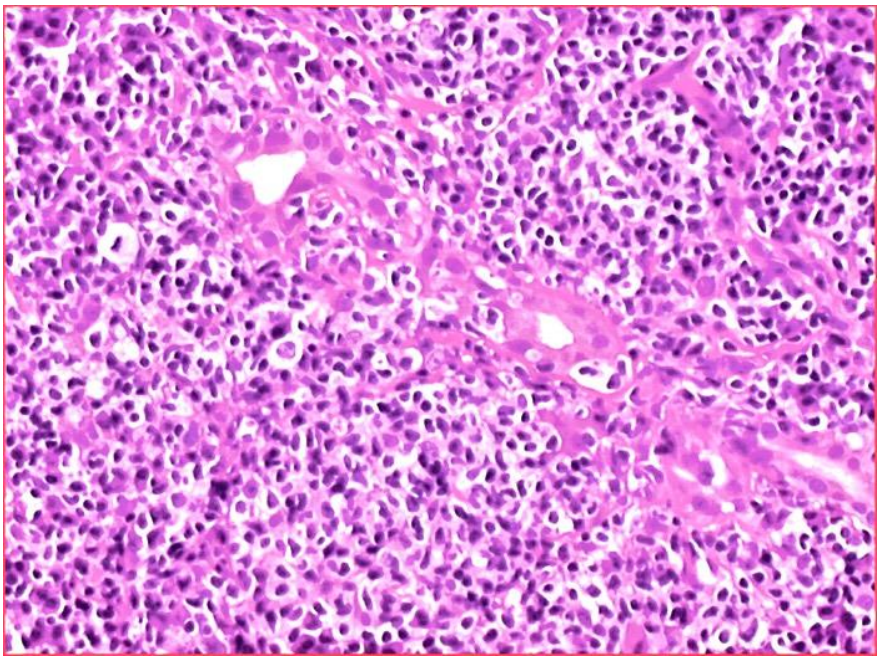

Figure 2: Lymphocytic destructive cholangitis

The other pantropic viral tests were irequested (Epstein Barr virus (EBV), Varicelle-zoster virus (VZV), Herpes simplex virus (HSV), Cytomegalovirus (CMV) because of the positive autoimmun tests and the acute cytolysis showing a high titers of serum globulin positive IgG at 12 and IgM at 5,13 (Normal<0,8) with a high viral load (> 3.7 log = 5483 UI/mL).

An immunodeficiency screening was conducted, which was normal with negative HIV, negative C3 and C4 complement test, and normal level of IgM, IgG , and IgA.

a search for the most frequentl sites involved by cmv infection has been initiated including colitis , encephalitis,uveitis, and pneumonitis and wad negative.

After these investigations, the selected diagnosis was a reactivation of CMV infection revealing a previously asymptomatic PBC at the end stage liver failure complicated by portal hypertension (PH), ascitis with a severity CHILD score at C10, and MELD score at 27.

The patient was treated for her PBC and PH with ursodeoxycholic acid, diuretics, and nonselective beta blockers (NNSB).

The patient was treated with Ganciclovir 5 mg/kg for 21 days that resulted in rapid improvement in clinical and biological status except for bilirubin which increase throughout the follow-up period.
the viral load was gradually reduced until it becomes undetectable 3 weeks after the start of treatment.

After 3 month, patient died from complications of her cirrhosis which was already at the end stage of liver failure.

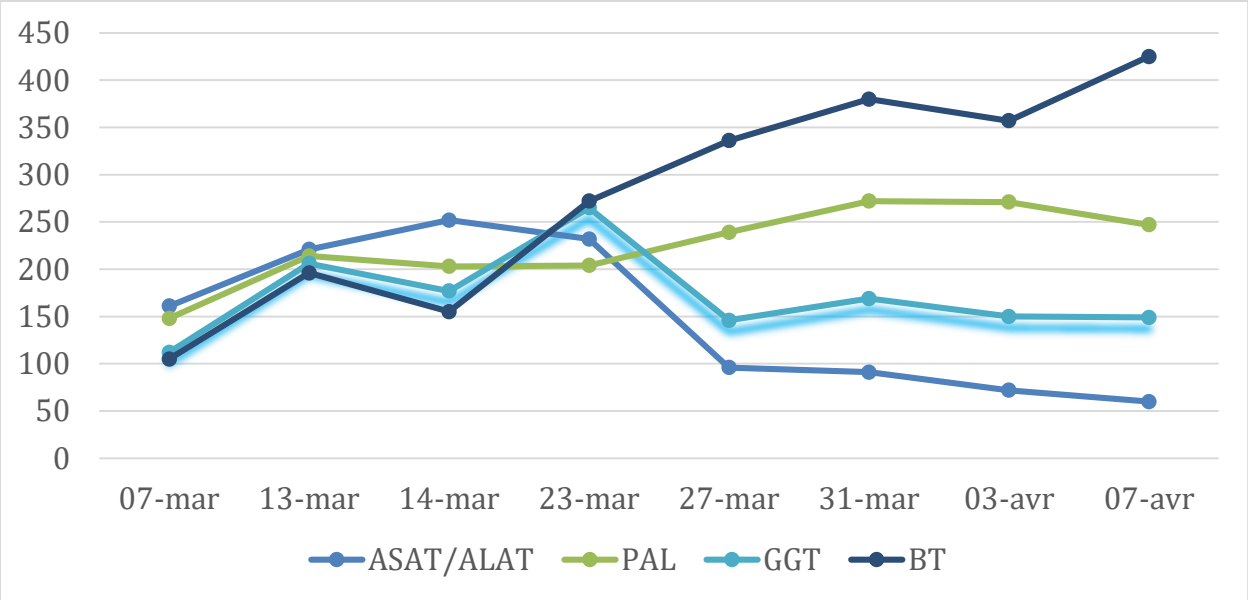

Figure 3 : Follow-up liver enzymes over 1 month

	J0 treatment	J14	J21
Viral load (UI/ml)	5484 UI/ml	Detectable but Non-quantifiable	undetectable

Figure 4 : The improvement of viral load before and after treatment

III. Discussion:

Infections with CMV are not rare and worldwide seroprevalence for CMV ranges from 60% to 100% **[3].** CMV remains latent in the body in most cases, however, in immunosuppressed individuals, CMV can present signs of target organ damage including enteritis, hepatitis, nephritis, pneumonia, meningoencephalitis, and retinitis accompanied by the presence of CMV in the tissues of the affected organ **[1-12]**

In immunocompetent individuals, it usually follows an asymptomatic course or presents with a mononucleosis-like syndrome **[2-3]** with fevers, presence of lymphocytosis with atypical lymphocytes, occasionally a rash, and abdominal pain. Furthermore, associated hepatic dysfunction and splenomegaly are common. however, in the literature, only 27 series of cmv-induced hepatitis in immunocompetent hosts have been reported, comprising a total of 43 patients. Half of them had but only 10 (23%) of them had jaundice on admission. **[4,5,7]** in our case the alarming sign was jaundice and fever.

Liver involvement by the CMV has been reported as hepatitis alone, granulomatous hepatitis, necrotizing hepatitis, and hepatic dysfunction associated with portal vein thrombosis.**13**

Immune reactions against host antigens are found to be the major pathologic mechanism. In fact, PBC might be associated with a number of other autoimmune diseases,1 but the exact mechanisms of onset remain unknown, but it can be explain that the immune system produces one or more types of autoantibodies, including antimitochondrial antibodies (AMA). **[14-15]**

Evidence suggests that PBC and alson autoimmune hepatitis is induced by antibody-dependent cell-mediated cytotoxicity, which involves both antibody-mediated and cellular immunity against specific liver antigens on hepatocyte membranes.2 Several studies have documented the involvement of genetic factors including human leukocyte antigen (HLA) types DR3 and DR4.3

retroviruses have been proposed as potentialtriggers of autoimmune diseases, including type 1 diabetes, Sjogren's syndrome and primary biliary cirrhosis. **[8-9]**

2 studies analysed the relationship between the presence of cirrhosis and cmv infection Toghill et al.71 analyzed 70 patients with cirrhosis caused by: alcoholic cirrhosis, , primary biliary cirrhosis, hemochromatosis,

drug-induced liver injury, secondary biliary cirrhosis, and cryptogenic cirrhosis .They did not find any evidence for CMV infection as the cause of liver disease. **[10]**

The seconde study of Faivre et al found the cause-and-effect relationship between cmv infection and cirrhosis and they concluded that CMV-seropositive cirrhotic patients were at higher risk of liver-related death caused by severe cirrhosis complications. which could explain the rapid and severe progression of advanced liver disease towards death in our patient. **[11]**

IV. Conclusion:

CMV infections are not commonly seen in immunocompetent adults and even less in association with an autoimmune liver disease.

In practice, when confronted with important disturbance liver function tests and positive immunological tests, nominal and pantropics virological tests must be formally excluded before considering a dysimmune origin of the hepatopathy.

This case is uncomon because these changes coincide or even precede CMV infection and appears to be a significant determinant of the prognosis of cirrhotic patients.

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