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Case Report

IMMUNE RECONSTITUTION IN LATE-PRESENTING HIV-POSITIVE A CASE WITH IDIOPATHIC LIVER CIRRHOSIS AND ISCHEMIC BRAIN STROKE

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Summary

A patient diagnosed with late-presenting HIV infection [CD4 count 86 cells/mm3, viral load (VL) 95 000 copies RNA/mL], treated with DRV/c 800/150 mg (Rezolsta®) and TDF/FTC 200/245 mg, was hospitalized with ischemic brain stroke, confirmed by CT scan and MRI. Motor functions quickly recovered, but nausea, abdominal heaviness, ascites, and hepatosplenomegaly appeared. Laboratory investigations revealed anaemia, thrombocytopenia, normal transaminases, increased GGT and negative serological tests for HBV and HCV and she was diagnosed with Gastroenterologists diagnosed liver cirrhosis. After 20 days of hospital treatment, the patient recovered from the stroke and ascites but with persisting anaemia and thrombocytopenia. Liver cirrhosis had been confirmed, and relevant treatment had been administered. Six months later, an MRI of the brain revealed an improved image. Follow-up showed stabilized somatic and neurologic status, improved laboratory parameters, stable T-helper count and undetectable viral load (VL). ART regimen continued with Raltegravir 400 mg (Isentress®) 2x1 tablet/24 h, TDF/FTC 200/245 mg 1 tablet/24 h. Three months later, the patient continued her treatment continued abroad. The increased access to precise diagnosis and treatment with improved adherence has transformed the HIV-infection into a manageable chronic health condition, even in complicated cases.

Keywords: HIV, ischemic brain stroke, liver cirrhosis, late-presenting, immune reconstitution.

Introduction

HIV is a public health problem with global significance. There are 36.3 million deaths registered so far [1]. Due to improved diagnostics, monitoring and treatment, HIV infection has become a manageable chronic health condition. Globally, previous 90-90-90 targets for 2020 were not achieved and the goal of less than 500,000 new infected annually and less than 500,000 deaths related to AIDS was not achieved in 2019. There were 1.7 million new infected and 600,000 AIDS-related deaths [2]. UNAIDS

launched the 95–95–95 targets in 2014: by 2030, 95% of all HIV-positive individuals have to be diagnosed, 95% of those diagnosed - to be on antiretroviral therapy (ART), and 95% of those treated - to achieve viral suppression [3].

The progress in controlling HIV spread, with a declined incidence in the past 20 years [4,5] and improved access to effective ART, is noticeable. However, there are specific problems in the therapeutic management of patients with HIV infection, especially in those with complications that are not directly related to HIV or possibly contributed by ART. Brain stroke is one of these complications. In middle-to-low-income countries, the incidence of stroke has increased by 100% during the past 20 years [6]. Probably, it is related to the ageing population and the increasing burden of vascular risk factors. Infectious causes of stroke might also contribute [7]. The highest incidence of HIV infection is in low-income and middle-income countries. Therefore, the simultaneous occurrence of both disorders is not rare. It is known that HIV infection affects the potential risk of stroke. The treatment of HIV can result in vascular damage, which confers an additional risk [6].

In clinical series, between 1% and 5% of HIV patients develop stroke, although 4–34% have cerebral ischemic lesions at autopsy. There was little correlation between both issues in a series that assessed pathological findings of cerebral ischemia and premortal clinical manifestations [7]. In the USA, hospital admissions of HIV infected with stroke had increased by 43% within nine years [8]. Despite this observation, few investigations have assessed the effect of HIV infection on the nature and burden of stroke. The pathogenesis of stroke in people with HIV is not fully clear. ART might also contribute to the risk of stroke by two causes: direct acceleration of atherosclerosis and increasing life expectancy [9]. Conventional vascular risk factors (hypertension, hypercholesterolemia, diabetes, cigarette smoking, and ageing) will continue to rise because people with HIV live longer. Moreover, continuous exposure to HIV (even at a lower titer of the virus) and chronic systemic inflammation might also be an additional risk of stroke [10].

Assessment of the impact of HIV infection on stroke is crucial, mainly focusing on the increased stroke frequency in regions with a high prevalence of HIV. As to the clinical practice, the management of patients with HIV and stroke requires taking into consideration that the cause, clinical presentation, and management of the stroke might be affected by the HIV infection and its treatment. On the other hand, in patients whose HIV status is not known, stroke might be the presenting feature of HIV infection [8,11].

Liver damage is another important aspect of HIV infection. Among persons living with HIV infection, liver disease is the typical result of co-infection with viruses of hepatitis B (HBV) or C (HCV). Alcohol abuse and hepatotoxic drugs also increase the risk [12]. The progression of liver disease in HIV-infected people was reporetd for the first time during the 1990s. However, the pathophysiological mechanisms, psychosocial problems, and comorbidities contributing to liver fibrosis have been elucidated in recent years [13-15]. Improved therapeutic regimens have been associated with a better course of the disease. The life expectancies of HIV patients now are similar to those of non-HIV-infected. However, many HIV-infected people are unidentified, and most of those with known HIV have persistent viremia. Liver disease in HIV infected leads to immune activation and liver fibrosis. The hepatic decompensation in HIV infection is more severe than in HBV or HCV without HIV. Currently, HIV care providers can offer newer direct-acting antiviral (DAA) HCV regimens, but the linkage between physicians managing people with HIV and hepatologists is limited in most places [16,17].

We present a rare, to our knowledge, HIV-positive patient with ischemic brain stroke and consequently diagnosed idiopathic liver cirrhosis.

Case presentation

An early-middle aged patient was diagnosed and confirmed HIV-positive after a continuous history of progressing wasting syndrome - daily sub-febrile temperature, weight loss and stomach discomfort. The patient had no history of past or present drug abuse and addiction. A possible way of transmission was sexual. The patient was diagnosed with epilepsy in early childhood, without clinical manifestations and no need for anticonvulsive therapy during her adolescence and adulthood. Allergies had

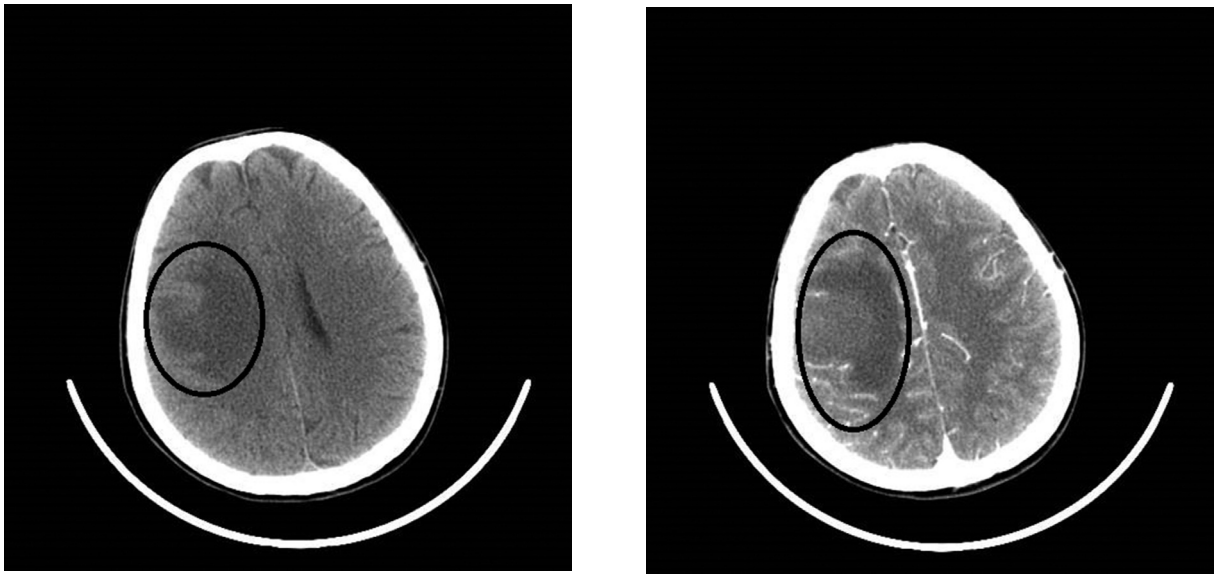
not been reported or registered. The patient was immunized according to the Republic of Bulgaria's mandatory vaccination calendar and did not receive HPV, HBV or Pneumococcal vaccines (all optional in Bulgaria).

Antiretroviral therapy was started immediately after confirming HIV status with Darunavir/c (DRV/c) 800/150mg x1tabl/24 h and Emtricitabine/Tenofovir disoproxil fumarate (TDF/FTC) 200/245 mg x1 tablet/24 h. The patient had immunologic characteristics of a late-presenting HIV infection with a baseline CD4 count of 86 cells/mm^3 and viral load (VL) 95, 008 copies RNA/mL.

The patient's first admission was with a prior diagnosis of ischemic stroke with left-sided hemiparesis and facial paresis, confirmed by native (Figure 1a) and contrasted CT scan (Figure 1b), MRI, and electroencephalography (EEG) (Figure 2).

On the day of admission continuous (approximately 20 min) generalized seizure without loss of consciousness appeared. The patiens was afebrile without signs of meningeal irritation, with no pathologic findings in the CSF sample. The follow-up and treatment were co-managed with a neurologist resulting in quick recovery of the motor functions and general condition. Despite that, on the 14th day of the hospital stay, the patient complained of nausea and heaviness in the abdomen. The physical examination revealed ascites, hepatomegaly (6 cm below the right subcostal margin), and splenomegaly (3 cm below the left subcostal margin). The abdominal ultrasonography demonstrated liver steatosis and fluid in the abdominal cavity. Laboratory examinations revealed haemoglobin (Hg) 87 g/L, erythrocytes (RBC) 2.8x10^{12}/L, platelets (PLT) – 31x10^9/L, GGT – 244 IU/L, normal transaminases (ASAT and ALAT) levels. Markers of HBV and HCV (HBsAg, anti-Hbc-total, anti-HCV) and the test for syphilis were negative. The patient was consulted and co-medicated (with diuretics and infusions of Human Albumin and plasma) by a gastroenterologist who diagnosed liver cirrhosis. After twenty days of hospital treatment, the patient was discharged with a fully-recovered neurologic status, without signs of ascites, with persisting anaemia and thrombocytopenia.

The patient was referred to a gastroenterologists for further laboratory and imaging investigations. A CT scan of the abdomen revealed enlarged liver with smooth contours and heterogenic structure in the portal-venous region, a single hypodense structure 4 mm in the IV segment, a portal vein up to 14 mm, contracted gallbladder and portal collateralization in the umbilical vein. The spleen was enlarged (transverse size in the hilum up to 50 mm). Multiple enlarged retroperitoneal lymph nodes up to 18/16 mm and free fluid in the abdomen had been



1a **1b**

Figure 1. Native (1a) and contrast (1b) CT scan image of hypodense zone in right temporo-parietal region (size 65/49 mm)

shown. FibroScan revealed liver cirrhosis, portal hypertension, ascites, and splenomegaly. Esophagogastroduodenoscopy revealed two short varicose columns in the distal third of the oesophagus. The conclusion made was for the presence of varicose veins of the oesophagus Ist grade. Tests for EBV VCA, CMV IgM, antinuclear antibodies (ANA), antimitochondrial antibodies (AMA) and anti-smouth-muscles-antibodies (ASMA) were negative. A liver biopsy was not performed because of persisting thrombocytopenia (36x10^9/L) and anaemia (Hg 89 g/L). Additional therapy was initiated with Livuron Forte, Ursofalc, Pantoprazole, Propranolol, Torasemide, Spironolactone, and Fero-Folgamma. She was on a strict diet and good drug adherence.

A control image study of the brain, performed six months later, revealed improvement. The patient had no pathologic neurologic signs or seizures.

Clinical follow up so far reveal stabilized somatic and neurologic status, without ascites. Laboratory follow up (Table 1, Table 2 and Table 3) revealed improvement of laboratory parameters, stable T-helpers count, undetectable VL in numerous investigations. Markers for viral hepatitis (HBsAg, anti-HBc-total, anti-HCV), fecal and oral swabs for Candida were negative in numerous investigations during follow-up. The patient was switched to another ART regimen with Raltegravir 400 mg (Isentress®) 2x1 tabl/24h + TDF/FTC 200/245 mg (Emtricitabine/Tenofovir) 1 tabl/24 h.

Three months later, the patient announced that she wanted to continue her treatment

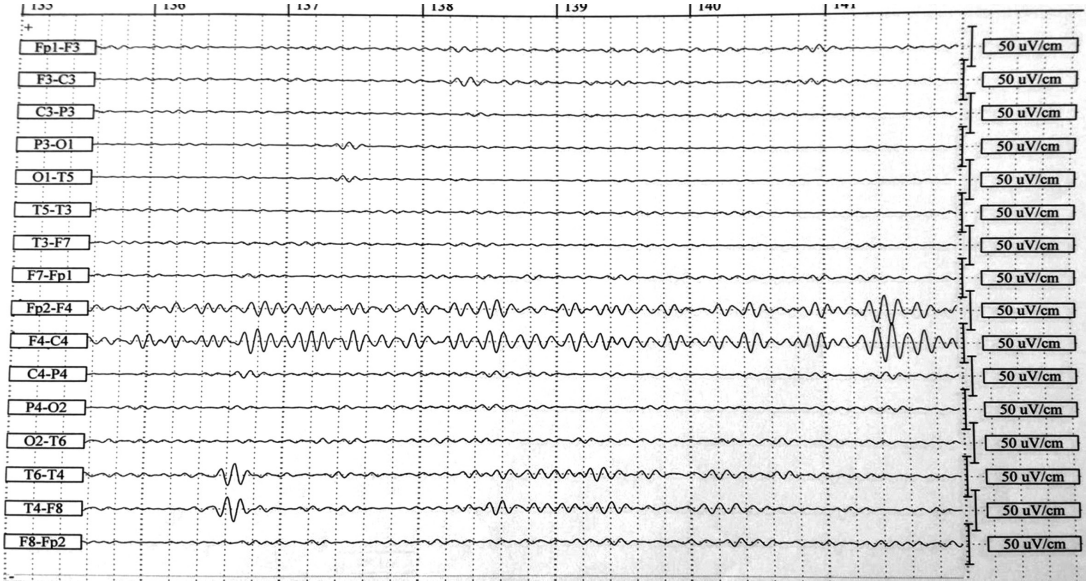


Figure 2. Paroxysmal focus with weak activity in right parietal-occipital region

Table 1. Laboratory control of blood cells

Date	RBC (3.7-5.9x10^{12}/L)	Hg (120-180 g/L)	Ht (0.35-0.45)	WBC (3.5-10.5x10^9/L)	PLT (150-360x10^9/L
20.05.18	**2.8**	**92**	0.27	5.4	**33**
18.06.18	3.2	104	0.30	2.0	**22**
19.09.18	4.0	130	0.38	3.3	**46**
21.11.18	4.2	137	0.40	3.6	**82**
04.06.19	4.4	137	0.41	5.6	168
03.12.19	4.5	143	0.43	6.9	211
13.05.20	4.4	142	0.42	6.3	233
07.12.20	3.6	119	0.34	10.7	211

Table 2. Laboratory control of biochemical laboratory parameters

Date	Cholesterol mmol/L (0.0 – 5.2)	Triglyceride mmol/L (0.0 – 2.3)	Creatinine µmol/L (53-115)	ALAT IU/L (0-40)	GGT IU/L (0-60)	CRP (0-5.0)
20.05.18	4.6	1.2	52	12	172	3.6
18.06.18	2.8	0.8	55	8		3.2
19.09.18	3.9	0.8	58	13		0.5
21.11.18	3.5	1.0	65	32		0.9
04.06.19	4.4	0.8	66	22		3.7
03.12.19	4.8	1.0	75	19	41	0.6
13.05.20	4.9	1.0	48	18	31	2.4
07.12.20	4.0	1.3	50	10		3.3

Table 3. Control of CD4 count, CD4/CD8 index and Viral load (VL)

Date	CD4 count cells/mm^3 (700-1100)	CD4/CD8 >1,0	VL copies RNA/mL
13.04.18	86	0,2	95008
19.06.18	217	0,7	
20.09.18	268	0,85	<40
19.12.18	240	0,6	
04.06.19	287	0,8	75
03.12.19	1174	0,9	<40
13.05.20	357	1,1	
02.10.20	260	1,4	<20

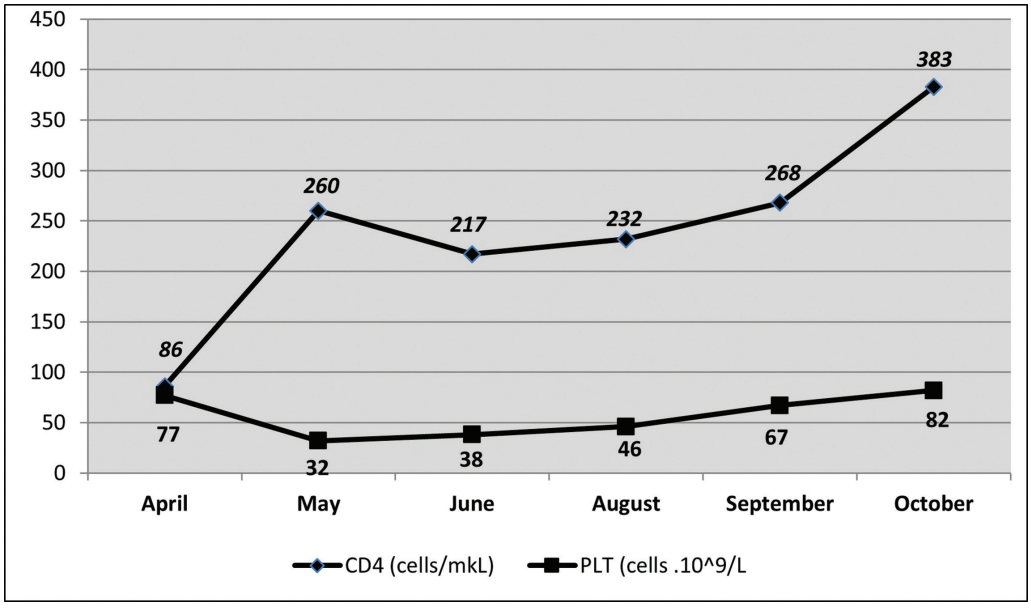


Figure 3. Monitoring of CD4 and PLT of the patient during 6-months period

and monitoring of HIV abroad, where she plans to live and work for a long time. Based on retrospective analysis of immunologic parameters (CD4 count, VL) and the platelets, we considered that the patient achieved immune reconstitution (Table 3, Figure 3).

Discussion

Brain stroke is among the complications of HIV- infected people, especially adolescents and young adults. The chronic course of HIV infection, ageing, and side effects of permanent ART and drugs have been considered leading causes for this trend. The increased prevalence of metabolic syndrome and comorbidities also have been connected with this complication [18,19].

The incidence of stroke in low and middle-income countries is increasing. Because HIV is prevalent in many of these regions, younger people are more likely to have infectious causes of stroke. It has been shown that HIV infection has the highest contribution to the overall burden of stroke in Malawi, where the population attributable fraction (PAF) is 15%. Behind hypertension, HIV infection was the second leading risk factor. HIV is the most critical risk factor among young patients with stroke (PAF is 42%). The initiation of ART might additionally contribute to stroke risk in immunosuppressed individuals [10]. Opportunistic infections, coagulopathy, and cardiothromboembolism are considered important etiologies [19-21].

Additionally, HIV infection leads directly to HIV- associated vasculopathy by inflammatory mechanisms. Vasculopathy is a hyperplasia of the intima more than can be expected for a certain age. Based on this statement, several pathologic phenotypes of stroke have been found in HIV infection – small vessel disease, HIV-associated vasculitis, HIV-associated atherosclerosis, and non-atherosclerotic vasculopathy (patients have non-vasculitis abnormalities, with hyperplasia of the intima that can progress later to stenosis or dilatation of an aneurysm). The pathologic mechanisms of these phenotypes are not well elucidated [10]. The case presented here is without a past history of cardiovascular disorders, and the hypothetic cause for the stroke could be connected with the liver cirrhosis diagnosed during the hospital treatment. ART has no connection because it started a month before the stroke.

Whether caused by alcohol, HBV, HCV, HIV, or other aetiology, the liver fibrosis progression is accelerated in HIV infected. There are different proposed mechanisms to explain why and to what extent ART increases the risk. It has been shown in a series of *in vitro* studies that the envelope of HIV triggers higher production of transforming growth factor-b1 by Huh7.5.1 cells. Thus, together with HCV, it enhances collagen and tissue inhibitor of metalloproteinase-1 production by stellate cells. By developing a co-culture system, it had been demonstrated that HIV and HCV independently activate the transforming growth factor-b1 signalling through reactive oxygen species (in both cell lines). Activating these pro-fibrotic pathways was additive after exposure to HIV and HCV. Expression of the pro-fibrotic genes was significantly higher in the co-culture model than in either cell type in monoculture. This suggests an interaction between LX2 and Huh7.5.1 cells. HIV exacerbates a pro-fibrogenic program in hepatocyte and hepatic stellate cell lines. This model is relevant to the HCV-related progression of liver fibrosis [14].

In vivo, HIV may affect other cell populations, such as Kupffer cells [8,9]. It is interesting because HIV infection has never been reconstituted with a virus obtained from Kupffer cells. At the same time, there is evidence that the total density of Kupffer cells might be affected [22]. HIV reduces the killing potential of intrahepatic natural killer (NK) cells. HIV also may reduce the ability of clusters of differentiation CD4 lymphocytes to restrain natural killer pro-fibrotic signalling [14]. It is not clear the extent to which ART promotes these mechanisms. However, even among patients receiving ART, a residual risk of liver fibrosis progression had been observed [22].

Increased translocation of gut microbial content is one of the potential mechanisms for promoting liver disease [22]. HIV infection has been associated with alterations in the gut microbiome. As a result, the pathogenesis of liver disease might be altered by enhanced translocation of some microbial products. By stimulating toll-like receptor 4 (TLR 4), lipopolysaccharide plays a role in the pathogenesis of non-alcoholic steatohepatitis (NASH) and acute liver disease (ALD). The final result is an inflammasome activation by enhanced signalling through myeloid-differentiation protein 88 (at NASH) or by TIR-domain-containing adapter-inducing interferon β (at ALD).

Moreover, HIV (and HCV) activate the

inflammasome and markedly increase the production of serum interleukin-18. It is unclear what the extent of synergism of these processes is; their mechanisms are also unknown. However, these explain certain extrahepatic manifestations of liver disease. For example, the incidence of cardiovascular disease increases with HIV and HCV, and macrophage activation has been linked to inflammation of carotid and coronary arteries [16]. Here presented case was a late-presenting HIV-positive but the good diagnostic and therapeutic interdisciplinary management led to immune reconstitution.

Conclusion

The increased access to precise diagnostic methods and treatment with improved adherence is transforming HIV infection into a manageable chronic health condition, even in complicated cases.

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