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Meningo encephalitis with Epstein-Barr virus in an immunocompetent adult patient: case report

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ABSTRACT

Epstein-Barr virus is a rare ethology of the neurological infections, expressed as encephalitis, aseptic meningitis, Guillain-Barre syndrome or acute demyelinating encephalomyelitis. Most common cases were reported in children, while this infection is rarely described in immunocompetent adults. We present the case of an elderly immunocompetent patient with hypertension and hypothyroidism under treatment who has presented to the emergency department for unusual headache, confusion, sudden loss of consciousness with retrograde amnesia, sudden onset for 2 hours associated with febrile respiratory symptoms. Traumatic neurological events, cerebral ischemia or metabolic encephalopathies were ruled out, while examination of the cerebrospinal fluid was positive for Epstein-Barr virus. The course of the meningoencephalitis was favourable, although an episode of diarrhoea with *Clostridioides difficile* with binary positive toxin A+B was notified. The primary infection or the reactivation of a previous infection, is a questionable mechanism of meningoencephalitis with Epstein-Barr virus in an old immunocompetent patient. According to the reported studies, the antiviral treatment with Acyclovir is controversial. The long-term prognosis of acute meningoencephalitis with Epstein-Barr virus is unpredictable and involves careful neurological and onco-haematological monitoring.

Keywords: Epstein-Barr virus, meningoencephalitis, *Clostridioides difficile*

INTRODUCTION

The Epstein-Barr virus (EBV) is a human herpesvirus, of the Herpesviridae family, with oncogenic potential, being involved in the pathogenesis of Burkitt's lymphoma, nasopharyngeal carcinoma, and other onco-hematological diseases [1].

EBV is usually transmitted orally, through saliva. The primary infection occurs frequently during the early childhood in the poor regions, while it is incident in adolescents and young adults from the developed regions. The EBV enters in the squamous epithelial cells, during the primary infection. After intracellular replication, the viral particles are released through transcytosis and infect naive B lymphocytes from the tonsils, being latent reservoirs with episodically reactivation and cytolytic consequences. The virus can also persist in the intestinal mucosa or meninges, but the role of these reservoirs is not clarified [2].

The clinical appearance of EBV infection is often asymptomatic or unspecific in children. Neurological complications of EBV infection are rare, with variable frequency between 0.4-7.5% of the cases reported in the literature [3].

Among the neurological manifestations attributed to EBV infection are encephalitis, aseptic meningitis, transverse myelitis, acute cerebellar ataxia, optic neuritis, Guillain-Barre syndrome or acute demyelinating encephalomyelitis. Most cases were reported in children, while the cases described in adults were mainly associated to immunosup-

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pressed patients with HIV infection, neoplasms or post-transplant [4].

Commonly, the prognosis of acute EBV meningoencephalitis (EEBV) is good, but the diagnosis could be difficult. Neuropsychiatric symptoms are usually inaugural indicators of EEBV, involving mental deterioration, reversible Parkinsonism, vasculitis and coagulation disorders [3]. EEBV lesions may interest the brainstem, cerebellum, thalamus, basal ganglia, optic nerve, or spinal cord [5].

The pathogenesis of neurological damage from EBV infection is not clarified until now. The mechanism of EEBV in children seems to be limited to the direct viral destruction of the neurons during the primary infection. This hypothesis is sustained by the absence of other usual manifestations of primary infection, such as tonsillitis, adenopathy, skin rashes or hepatosplenomegaly, but also by the recovery of neurological symptoms and the clearance of viral DNA from the cerebrospinal fluid (CSF). Other pathogenic mechanisms related to EEBV are the autoimmunity, due to the similar structure of some viral antigens and the glycoproteins of the myelin oligodendrocytes, or the viral reactivation from the latent reservoirs in immunosuppressed patients [6].

CASE REPORT

A 72-year-old patient, urban living, was presented to the emergency department for unusual headache, confusion, sudden loss of consciousness with retrograde amnesia, sudden onset for 2 hours. One day before, she presented febrile respiratory symptoms. The medical history revealed surgery for L4-L5 disc herniation, blood hypertension and hypothyroidism under current treatment with Candesartan, Indapamide, Carvedilol and Levothyroxine. She denied previous COVID-19 history but over one year ago she received two shots of Pfizer-BioNTech COVID-19 vaccines. The seasonal flu vaccine was updated [Figure 1].

The clinical examination revealed: lumbar post-surgical scar, kyphoscoliosis, fever of 39°C, Glasgow score 11, blood pressure 170/110 mmHg, heart rate 95/min respiratory rate 20/min, peripheric oxygen saturation 97%, mixed aphasia, mild intensity of meningeal clinical signs, but no focal neurological deficit.

The native cerebral computed tomography (CTC) revealed sequalae of periventricular bilateral hypodense small lacunae. The cerebrospinal fluid (CSF) had bloody appearance. The lab characteristics were pleocytosis with 1000 cells/mm^3, 70% lymphocytes, 30% polymorphonuclear, mild increase of albumin (66 mg/dl), and normal glucose (52 mg/dL). No other CSF investigations were available on that moment.

Pulmonary X-ray described bilateral accentuation of the interstitial space, minimal left pleural effusion and cardiomegaly [Figure 2 a, b].

Traumatic neurological events, cerebral ischemia or metabolic encephalopathies were ruled out and she was admitted to the infectious diseases ward in the next 12 hours. She was still febrile with

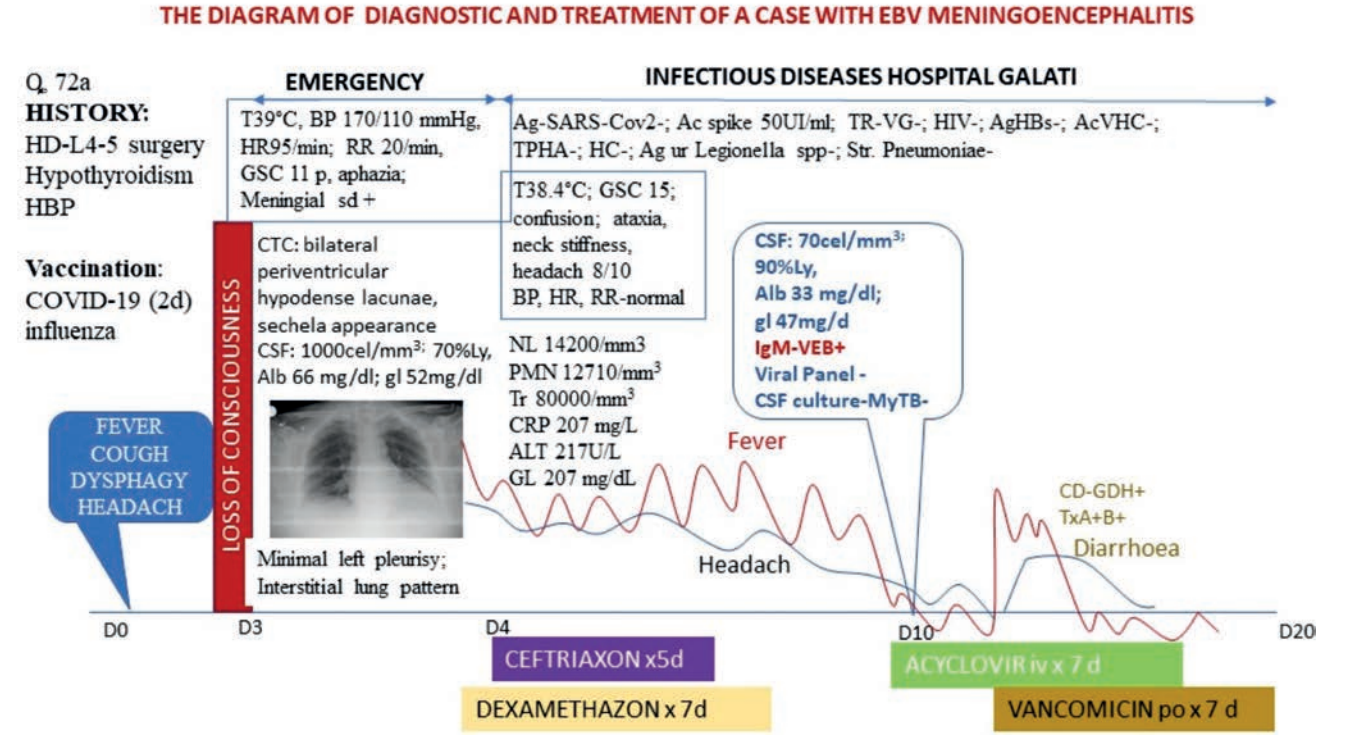
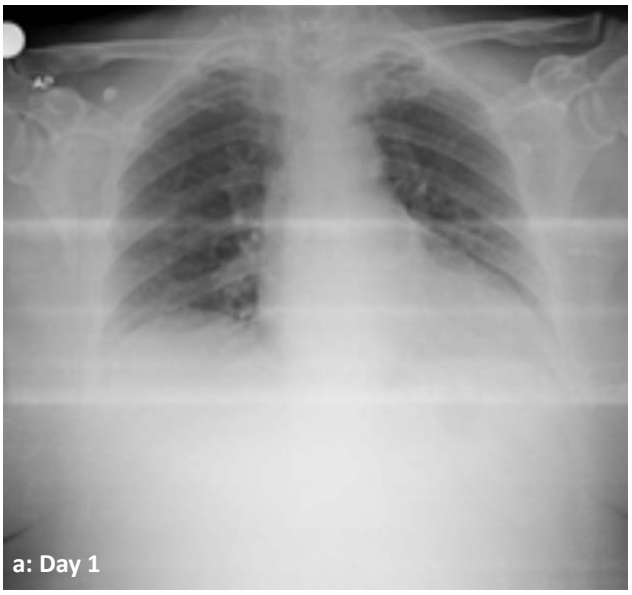


FIGURE 1. Evolution of the meningoencephalitis with Epstein-Barr Virus in an old adult immunocompetent patient



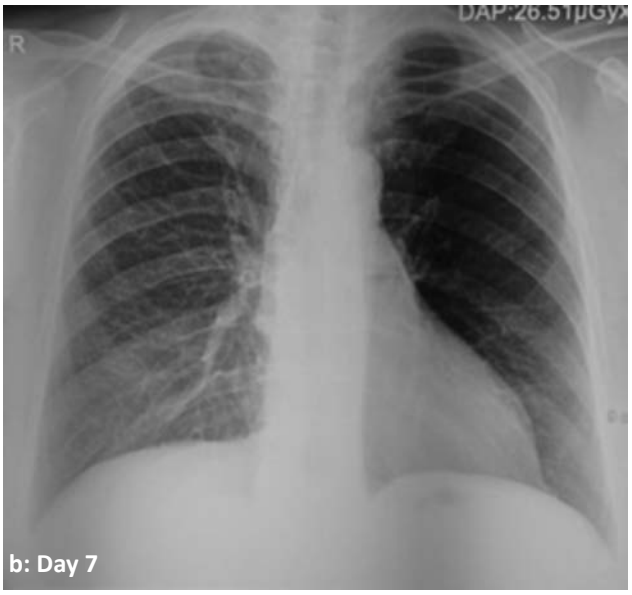


FIGURE 2 a, b. Dynamic of pulmonary X-Ray

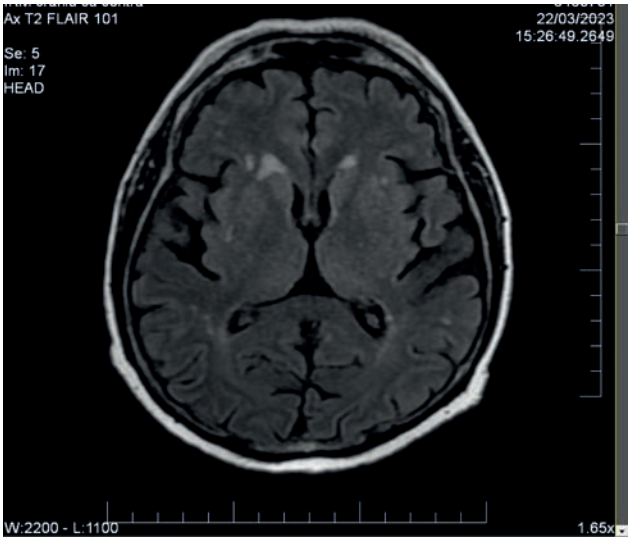
a temperature of 38.4°C, confused but conscious, cooperative, Glasgow score 15, moderate nuchal stiffness and cerebellar ataxia. Blood pressure, heart rate and respiratory rate were normal, but headache (8/10), dry cough, diffuse abdominal pains and diarrhea were notified.

The tests for influenza, SARS-CoV-2, HIV, hepatitis A, B or C viruses, syphilis, were negative. The level of anti-Spike antibodies of SARS-CoV-2 was 50 UI/ml (normal range 0-10 UI/ml). Urine antigens for *Streptococcus pneumoniae* or *Legionella pneumophila* were negative.

The lab results specified leucocytosis with neutrophilia, anemia, thrombocytopenia, inflammatory syndrome, hyperlactatemia, increased procalcitonin, increased liver enzymes and hyperglycaemia. A new lumbar puncture was not available, but the hematology, biochemical tests and the pleurisy have counted for the suspicion of a bacterial infection and antibiotic treatment with Ceftriaxone [Table 1]. However, headache and fever persisted.

Blood, cerebrospinal fluid (CSF) and stool bacterial and fungal cultures prevailed at hospital admission continued negative.

A lumbar puncture was repeated. The CSF examination pointed 70 cells/mm^3, glucose 47 mg/dl, albumin 33 mg/dl and the BioFireFilmArray Meningitis/Encephalitis Panel was completed. The test for EBV was positive. Negative results were found for qRT-PCR for *Mycobacterium tuberculosis* complex, and the tests for Human herpes viruses [1,2,6,7], *Varicela-zoster virus*, *Cytomegalovirus*, *Parvovirus B19*, *Mumps virus*, *Enterovirus, Parechovirus*. Acyclovir and a Dexamethasone followed for a course of 7 days, while the antibiotic was discontinued. Fever and neurological symptoms were remitted.



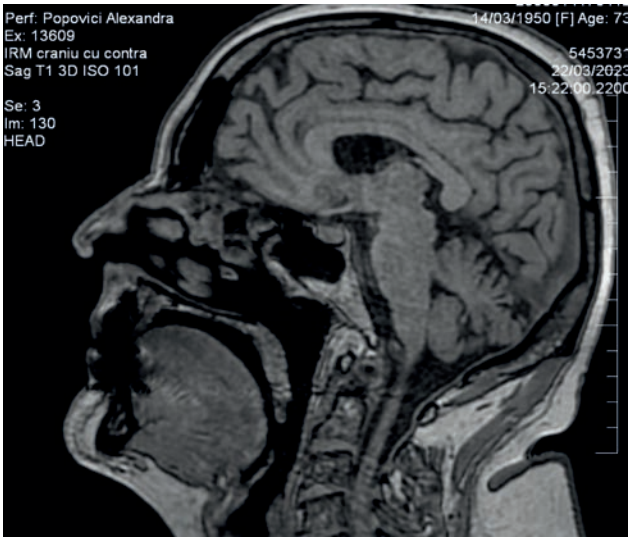


FIGURE 3. The Magnetic Resonance Imaging a – coronal section T2 Flair; b – sagittal section

The brain MRI revealed left frontal ischemic gaps, cortical atrophy, bilateral fronto-parietal demyelinating lesions [Figure 3 a, b].

Meanwhile, the frequency of the diarrheal stools increased and the repeated tests for glutamine-dehydrogenase and Toxin A+B of *Clostridioides difficile* were positive. Favorable evolution of diarrhoea was achieved after diet, rehydration and 7 days of Vancomycin.

The patient was clinical recovered and was discharged after 14 days of hospitalization. Hyponatremia in the clinical context require the investigation for the antidiuretic hormone, considering postencephalitic risk of developing the syndrome of inappropriate antidiuretic hormone secretion [Table 1; Figure 1].

DISCUSSIONS

Meningoencephalitis with EBV is rarely described in adults without immunosuppression. Age could be a frail condition related to the decrease of the immune response, although we have not identified any immunosuppressive disease or therapy in our reported case.

The old age, the cardiovascular co-morbidities and the presentation with pleurisy were the main interferences of the difficult analysis of the symptoms and differential diagnosis, as stroke, brain tumours, tuberculous encephalitis, other immune or degenerative neurological diseases.

The explanation of the EBV positive test in the CSF was dilemmatic, either a primary infection that is unusual in an elderly individual, or a reactivation of an old persistent infection. [7]

In a 10 years retrospective study on 780 CSF samples, there were identified 6.2% immunocompetent patients with positive samples for DNA-EBV PCR, but 22.7% of them were co-infections with other viruses or bacteria. The results possible to reflect either the reactivation of EBV by some co-pathogens or the contamination the CSF through infected B lymphocytes, but not the real aetiology of the current neurological infection [8,9].

Several epidemiological, serological and virological studies proved the relationship between EBV and the immune dysfunction specific of multiple sclerosis. However, the aetiology of multiple sclerosis is multifactorial, and the results of some studies are unexplained or controversial [2].

These data sustain the cautious medical interpretation and the necessity to follow up the patient, regarding the development of lymphomas, multiple sclerosis or other long time neurological complications.

The cytolytic syndrome associated with EBV meningoencephalitis can be explained by the liver tropism of the virus, either during a primary infection or by viral reactivation, but potential liver toxicity of the medication could be also involved [10].

The association of diarrhea with *Clostridioides difficile*, favored by the use of cephalosporins and the risk of hospitalization, corresponds to the case definition for healthcare-associated infections. In addition, a possible interference on intestinal dysmicrobism, of active/reactivated EBV infection, can be speculated, supported by studies that have demonstrated its role in inflammatory colitis [11-13].

A specific guideline for the treatment of meningitis and EEBV is not available, that is based on symptomatic and supportive interventions. The role of corticosteroids is controversial but could be more beneficial in the case of immune neurological pathogenesis. The role of intravenous immunoglobulins in the treatment of viral encephalitis is currently unclear due to the limited scientific evidence of efficacy and clinical benefit [14]. Rituximab, is an anti-CD20 monoclonal antibody that targets B lymphocytes, has been tested in severe EBV infections and is a potential therapeutic option [15].

The nucleoside analogues antivirals (acyclovir, penciclovir, ganciclovir) and their derivatives (valacyclovir, famciclovir, valganciclovir), the nucleotide analogues (cidofovir) and pyrophosphates (foscavir) are approved for the treatment of herpes simplex virus 1 (HSV-1) and 2 (HSV -2), varicella-zoster virus (VZV), and/or human cytomegalovirus (HCMV). These drugs have experimentally proved in vitro effective inhibition of EBV replication [16].

The use of antivirals in clinical practice evidenced limited clinical therapeutic effects, and none of them was approved for the treatment of EBV infections by Food and Drug Administration or European Medicines Agency [17].

Various phases of clinical trials for EBV treatment are evaluating antivirals as inhibitors of EBV Protein Kinase BGLF4, inhibitors of EBV-DNA polymerase, inhibitors of EBV nuclear antigen 1 (EBNA1), selective inhibitors of nuclear export (Verdinexor), topo II catalytic inhibitors (novobiocin, merbarone, rutamarin) [17].

The perspectives of developing an anti-EBV vaccine are still limited [18].

CONCLUSIONS

EBV infection is a cause of viral meningoencephalitis, even in apparently immunocompetent elderly people. The treatment of EBV meningoencephalitis with Acyclovir had a favorable outcome, although skeptical results are reported by other studies and the clinical data are limited. The long-term prognosis of acute meningoencephalitis with EBV in an elderly person is unpredictable and requires careful neurological and onco-hematological monitoring.

TABLE 1. Dynamics of biological and imaging data in the patient with EBV meningoencephalitis

	Normal values	Day 1	Day 2	Day 5	Day 6	Day 7	Day 14
Blood							
WBC [x10^3/uL]	4-10	14800	14200	9600	14200	17000	9100
Neutrophils	2.00-7.50	11500	12710	6060	11050	13940	5910
Lymphocytes	1.00-4.00	1720	890	2430	1630	2070	2500
Hemoglobin [mg/dl]	11.5-16	12.8	12.4	10.7	11.7	10.1	11.7
Platelets[x10^3/uL]	150-450	109	80	133	164	208	323
CRP [mg/L]	0-5		207	64	62		4.15
ERS mm/h	0-15		46	100	100		42
Procalcitonin [ng/ml]	negative		1.54	0.20			
Lactate [mg/dL]	4.5-20		24	10.85	23		
ALT U/L	0-34	63	46	217	198	160	172
AST U/L	0.31	47	29	105	81	86	58
Bilirubin-Total [mg/dL]	0.0-0.20	0.88		0.36			0.42
GGT[U/L]	0-55			39			366
Albumin g/dL	3.5-5.2		4,34		3.90	3.60	3.97
D-DIMERS ng/mL	0-500			1176	1112		648
Ferritinng/mL	*30-350*			648			355
Urea mg/dL	19-44	31	35.5	34		67	44
Creatinine mg/dL	0.80-1.30	1.28	1.20	1.13		1.17	0.99
Glucose mg/dL	74-106	118	205	97	98	140	95
Cl- mmol/L	98-107	110	104	102	99	105	105
K+ mmol/L	3.5-5.3	3.50	3.4	4.1	4.2	4	3.7
Na+ mmol/L	135-148	145	139	140	138	138	139
CSF							
Cell count/mm^3	0-4	1000				70	
Monocites%		70				90	
PMN%		30				10	
Albumin mg/dl	16-30	66				33	
Glucose mg/dl	50-70	52				47	

Legend
ALT: Alanine aminotranspherase; AST: Aspartate aminotransferase; ERS: Erythrocyte sedimentation rate; CRP: C-Reactive Protein; GGT: Gamma glutamyl transpeptidase; WBC: White Blood Cells count

Conflict of interest: I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work.

Statement on Human and Animal Rights

I undersign and certificate that the research conducted complied with the ethical standards in accordance with Helsinki Declaration (of 1975, revised in 2013), as well as national regulations in the field.

Statement on informed consent

I undersign and certificate that I have obtained the written consent of the identified persons or their legal guardians for the presentation of the cases within the present scientific paper.

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