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Case Report

Encephalitis on an Immunocompromised Patient Following COVID-19 Vaccination Causal or Coincidental Correlation

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ABSTRACT

The COVID-19 pandemic has made a major impact worldwide. The vaccines production was a huge biotechnology achievement empowering the defense against this fatal threat. However, as billions of shots have been administered, some safety issues have been raised. We present a case of a 55-year-old patient with a history of CLL (Chronic Lymphocytic Leukemia), who had encephalitis seventeen days post vaccination. Although the benefits outweigh the risk of vaccination at this point, all the rare and serious adverse events should be reported. The significance of such reports is even greater when refer to special patient sub-groups, regarded as immunocompromised.

Keywords: Encephalitis; COVID-19 vaccination; Leukemia; Adverse events; Rash; Seizures

INTRODUCTION

It has been two years from the COVID-19 pandemic outbreak. SARS-CoV-2 was first reported in December 2019. On December 23, 2021, there have been 278.137.089 confirmed cases and 5.386.290 COVID-19 related deaths. In December 2020, the first COVID-19 vaccines received emergency use authorization in the United States. Since then, 8.806.100.479 of doses of vaccine have been administered worldwide empowering humanity's defense against this infection [1]. However, in some cases, adverse effects after receiving COVID-19 vaccination have been reported [2]. These events are mostly mild and temporary, but there are also rare reports of serious even fatal adverse events related to the COVID-19 vaccines. Serious neurological adverse events are quite rare but can occur [3]. The physicians should be aware to recognize, report and treat early any adverse event after vaccination. We present the case of a 55-year-old male patient with encephalitis 17 days post vaccination who had Chronic Lymphocytic Leukemia (CLL) in remission. Based on our case, we would like to present all the challenges that this special sub-group of hematologic patients may have regarding their immunization protocol.

CASE PRESENTATION

We present a 55-year-old patient who was admitted to the emergency department on the 29th of May 2021 with 24-hours history of fever, agitation, confusion, headache, and vomiting, without nuchal rigidity. His partner reported the patient had an episode of consciousness loss along with convulsions in keeping with GTC (Generalized Tonic-Clonic) seizures. The episode occurred an hour prior to his admission.

There was no known prior COVID-19 exposure. RT-PCR tests (COVID-19 Reverse Transcriptase-Polymerase Chain reaction) were performed on two occasions; on the day of the admission and the day before, which were both negative. Regarding his past medical history, the patient was diagnosed with Chronic Lymphocytic Leukemia (CLL) two and a half years ago, for which he was on treatment, and he has been in close monitoring by his hematologist; on remission since 2019.

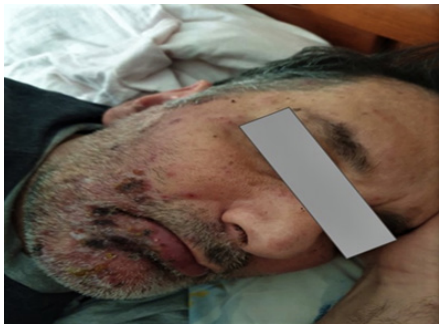

Figure 1: A herpetic vesicular rash is present on the V3 nerve branch distribution. Picture was taken on the 7th of March 2021, 3 months prior to hospital admission.

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We present the timeline of the preceding clinical events: The patient had a herpetic, vesicular rash on the trigeminal nerve (V3 area distribution) three months ago and was treated with oral valacyclovir in the community shown in Figure 1.

He was fully vaccinated with Pfizer BioNtech COVID-19 having received the first dose on the 10th of April and the second dose on the 7th of May. A week after the second dose a whole-body patchy urticarial rash appeared, which was treated with oral corticosteroids and antihistamines for ten days. The fever and confusion occurred after the cessation of the aforementioned medication shown in Figure 2.

Figure 2: Timeline of the clinical events occurred until the day of the admission (27/05).

The clinical hypothesis was of an acute encephalitis. An emergency NCCT (Non-Contrast Computed) scan was performed without acute findings, followed by a LP (Lumbar Puncture) under sedation due agitation. The CSF (Cerebrospinal Fluid) showed 855-858 cells (Lymphocytes), CSF protein 117.9 mg/dl and CSF glucose 46 mg/dl.

He was empirically treated for encephalitis with Dexamethasone (1 amp 8 mg stat), Acyclovir (750 mg iv tds), Ceftriaxone (2 gr iv bds), Vancomycin (1 gr iv bds), and Levetiracetam (500 mg bds).

Due to extreme agitation, he was intubated and remained in the Intensive Care Unit for four days. His treatment was adjusted accordingly after the CSF PCR and culture results, which came back negative. Therefore, we only treated him with antiviral treatment. We also tested the CSF for WNV (West Nile Virus), negative result. An MRI (Magnetic Resonance Imaging) scan was performed showing unremarkable findings shown in Figure 3a and 3b. The EEG (Electroencephalogram) did not reveal epileptiform abnormalities. Intermittent slow delta waves were recorded in frontal and central areas bilaterally, with left side predominance shown in Figure 3c and 3d.

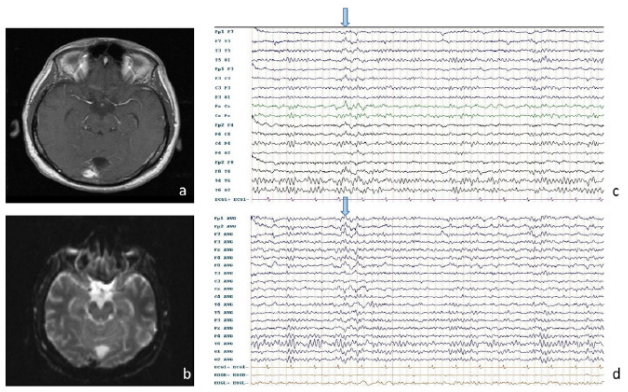

Figure 3: MRI: T1Gd (a) and diffusion weighted imaging sequence (b) show no meningeal enhancement nor parenchymal lesions. EEG: (c) Bipolar montage Intermittent slow delta waves were recorded in frontal and central areas bilaterally with left side predominance, with normal background activity. (d) Average reference montage for the same area/activity (blue arrow).

The patient was extubated, and he was transferred back to the neurology ward. He was fully orientated and there was no neurological deficit.

We performed a second LP, which showed a marked improvement on WBC (White Blood Cell) count. Again, there were no pathogens to be found in the CSF. Interestingly, the cytologic examination of the CSF revealed inflammatory process; high albumin and presence of oligoclonal bands type II observed in Table 1.

Table 1: CSF analysis, culture, and antibody testing.

CSF analysis	29/05/2021	8/6/2021	Normal values
Colour/Clarity	Clear fluid	Clear fluid	
WBC Count	855-858 (lymphocyte type)	332-333 (lymphocyte type)	0-5 leukocytes per mm3
Albumin(mg/dl)	117.9	47.9	15-45 mg/dl
Glucose(mg/dl)	46	54	40-70 mg/dl
PCR CSF	Negative	Negative	
Culture	Negative	Negative	
Antibodies*	Negative	Negative	
Oligoclonal bands (OCBs)		Type II	

Note: *Tested for CMV (Cytomegalovirus), EBV (Epstein -Barr Virus), HSV (Herpes Simplex Virus), VZV (Varicella Zoster Virus) IgM/IgG antibodies.

Since the initial clinical manifestation was typical of viral/possibly herpetic encephalitis and towards the investigation of viral encephalitis with no pathogens to be found on the CSF, we also sent CSF and serum samples for N-Methyl-D-aspartic acid (NMDA) IgG receptor antibodies, which also came back negative observed in Tables 2 and 3. Taking into consideration of the CSF and blood tests results, the Infectious Diseases Specialists suggested a total 14-days course of acyclovir intravenously. After the intravenous treatment the patient received antiviral prophylaxis as an immunocompromised patient.

Table 2: Immunoglobulin and complement titers.

Serum	Values	Normal values
Total IgG(mg/dl)	296	751-1560 mg/dl
Total IgA(mg/dl)	29	82-453 mg/dl
Total IgM(mg/dl)	30	46-304 mg/dl
Total IgE(mg/dl)	10.9	22-165 mg/dl

Serum protein electrophoresis	Widespread immunoglobulinaemia	
C3(mg/dl)	190	79-152 mg/dI
C4(mg/dl)	55.5	16-38 mg/dI
Sars Covid IgG	7.4	<50 AU/ml

Table 3: Serum antibody titers.

Serum antibodies	Values	Normal values
West Nile Virus IgM	Negative	
N-Methyl-D-aspartic acid (NMDA) receptor IgG	Negative	
Cytomegalovirus (CMV) IgM	Negative	<0,85 index
Cytomegalovirus (CMV) IgG	Negative	<6 AU/ml
Herpes Simplex Virus (HSV) IgM	Negative	<0,9 AU/ml
Herpes Simplex Virus (HSV) IgG	Positive (79.3 AU/ml)	<0,9 AU/ml
Varicella Zoster Virus (VZV) IgM	Negative	<0,9 AU/ml
Varicella Zoster Virus (VZV) IgG	Positive (106.4 AU/ml)	<0,9 AU/ml

Follow up

Four months after the discharge, the patient is without focal neurological impairment, and he remained on antiviral prophylaxis with valacyclovir. However, due to inguinal lymphadenopathy the patient underwent PET-CT (Positron Emission Tomography and Computed Tomography) scan, and the results were suggestive of relapse of CLL, possibly RS (Richter's Syndrome). In contact with his hematologist, he suggested CAR-T (Chimeric Antigen Receptor-T cell) treatment therapy initiation. If the patient responds poorly, then he is a candidate for stem cell implantation.

RESULTS AND DISCUSSION

To our knowledge, this is an interesting case of encephalitis temporally related with COVID-19 vaccination.

Our case presented with clinical signs of viral encephalitis 20 days after COVID-19 vaccination. Although the timeline of clinical events would suggest a VZV infection recurrence, no infectious agent was isolated. In favor of a Herpes virus infection was the CSF laboratory results and the excellent response treatment to acyclovir. Several viruses have a propensity to replicate and/or reactivate under conditions of immunosuppression causing neurological disease. These viruses include HSV-1, HSV-2, VZV, CMV, EBV and HHV-6 (Human Herpes Virus type 6) as well as JCV (John Cunningham Virus), enteroviruses, measles, and the novel coronavirus COVID-19 [4]. VZV is a neurotropic virus that, on primary infection, resides and remains latent in dorsal-root or cranial-nerve ganglia. Reactivation of VZV leading to the clinical manifestations seen in herpes zoster may then ensue spontaneously, following activation by a trigger, such as trauma, fever, or immunosuppression [5]. There have been reports of Herpes simplex virus infection recurrence related to the COVID-19 vaccines attributed to post-vaccination stress, increasing age, and immunocompromised condition [5-9].

Despite the fact that our patient was in CLL remission, he was considered to be immunocompromised by his hematologist and therefore in a high-risk population of COVID-19 infection. Recent metanalysis suggests that there is a significant protective effect against RT-PCR confirmed COVID-19 [vaccine effectiveness of 95% (95% confidence interval: 96%-97%)]. There have been limited data about vaccine effectiveness among immunocompromised patients; thus, the vaccine should be used cautiously in this patient population [10,11]. The immunization of our patient was ineffective, raising questions regarding the immunization process in this high-risk population and the risk-benefit balance out of it. Recent literature data regarding COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia suggest that patients with CLL should continue to be cautious following vaccination until further data on clinical efficacy are available. Furthermore, current reports present disparity regarding antibody responses [12-15].

According to our patient's recent medical history, someone would have proposed the possibility of immunization against VZV via vaccination. However, in Greece, only a live attenuated varicella vaccine is available, and this was not a suitable option for our immunocompromised patient, while the role of zoster vaccination for the immunocompromised patient is currently not established [4]. At his status is advised to use chemoprophylaxis indefinitely. Adverse events (AEs) following immunization may be a coincidental phenomenon or may be causally related to the vaccination.

CONCLUSION

In our patient, the viral encephalitis could have a causal correlation, considering his immunocompromised status, the preceding steroid treatment, and the subsequent COVID-19 vaccination as trigger agent.

This case should raise awareness regarding the need of chemoprophylaxis and the further investigation on this high-risk population regarding COVID-19 immunization efficacy, safety, and right timing. Infrequent manifestations of COVID-19 vaccine-related neurological complications are indeed possible. Although serious adverse reactions to vaccines are rare, should be, reported, and investigated to facilitate the ongoing safety evaluation.

DECLARATION

Ethical approval

All procedures performed in this study were in accordance with the Helsinki declaration.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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