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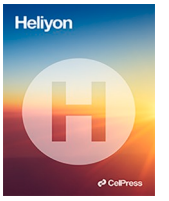

Case report

Disseminated herpes zoster with varicella encephalitis and pneumonia following ChAdOx1 nCoV-19 (AZD1222) vaccine in an immunocompetent male-a case report

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ABSTRACT

A middle-aged gentleman, presented to our outpatient department with painful skin lesions suggestive of disseminated herpes zoster. Further examination revealed bilateral cerebellar signs. He had a history of receiving a third dose of AZD1222 vaccine fourteen days prior to the onset of skin lesions but had no other significant medical history. The patient was also evaluated for retroviral infection and other immunodeficient states, workup for which were negative. The patient was initially treated with intravenous acyclovir 7.5 mg/kg/q8H; however, the patient developed varicella encephalitis on treatment, which was followed by pneumonia and haemorrhagic cystitis. Subsequently, treatment was started with acyclovir 10 mg/kg/q8H for 14 days, followed by valacyclovir for eight days, following which there was near-complete resolution of symptoms with the persistence of minimal rigidity. Although there have been several reports of herpes zoster following SARS-CoV-2 vaccination, we found few reports of varicella zoster with systemic manifestations following ChAdOx1 nCoV-19 (AZD1222) vaccination. This case highlights the importance of considering varicella zoster reactivation in a patient presenting with encephalitis or pneumonia post SARS-CoV-2 vaccination.

1. Introduction

The SARS-CoV-2 pandemic has necessitated the urgent development and rollout of vaccines to limit disease-related mortality and morbidity. Although the spectrum of systemic complications following vaccination is wide, their incidence itself is relatively low. An initial phase 1/2 trial evaluating the safety of the ChAdOx1 nCoV-19 (AZD1222) vaccine revealed no significant systemic adverse effects [1]. Although there have been several reports of varicella zoster reactivation post-vaccination [2], severe systemic reactivation has mainly been reported following mRNA vaccines and is very rare following inactivated or viral vector vaccines. Here, we discuss the case of a middle aged, immunocompetent man who presented with disseminated herpes zoster following the AZD1222 vaccine (replication-incompetent adenoviral vector vaccine) and developed varicella encephalitis with pneumonia.

2. Case presentation

A 57-year-old South-Asian man presented to our outpatient department with a history of fluid filled vesicular lesions over the

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bilateral upper abdominal quadrants, associated with burning pain, for which he had received oral acyclovir (500 mg three times daily) at a local hospital. Following this treatment, the lesions had initially resolved; however, the patient later developed superficial ulcerations over the right upper abdomen with crusting and complained of persisting burning pain over the site of lesions, more on the right than the left side. Additionally, the patient had a history of swaying while walking for 5 days and persistent hiccoughs for 2 days. Detailed medical history revealed none of the following: comorbidities, history suggestive of autoimmune disease, varicella infection, zoster, immunization against varicella zoster, history of long-standing constitutional symptoms preceding the current illness, history of recurrent infections, use of alternative or herbal medicines. The only positive history observed was that the patient had received a third dose of the AZD1222 vaccine 14 days prior to the onset of the skin lesions.

Upon clinical examination, the patient was hemodynamically stable. Superficial ulcerations over the right T9-T10 dermatomal distribution with areas of haemorrhagic crusting were present, suggesting disseminated herpes zoster (T9-T10). Bilateral cerebellar signs were noted; however other neurological and systemic examination normal. Contrast-enhanced magnetic resonance imaging of the brain revealed no significant abnormalities. We made a provisional diagnosis of disseminated herpes zoster with cerebellitis, and initiated intravenous acyclovir at 7.5 mg/kg q8H. The patient initially received ceftriaxone, which was later discontinued.

Baseline investigations showed normal leucocyte counts and normal renal and liver functions, with hyponatremia(euvolemic) of 98 mmol/L, which was corrected over a period of five days at a rate of 8–10 mmol/day. On the fifth day of the acyclovir treatment, the patient started to become progressively disoriented and drowsy, with new-onset rigidity involving initially the upper limbs, then lower limbs and bilateral extensor plantar response. An urgent repeat brain MRI was performed to rule out osmotic demyelination which showed T2 and FLAIR hyperintensities involving the caudate and lentiform nuclei (see Fig. 1). A CSF analysis was performed, which showed 15c/cmm (lymphocyte predominant) with varicella zoster PCR positivity (Realstar VZV PCR Kit 1.0) and other infectious workup negative, confirming varicella encephalitis.

Acyclovir was administered at a dose of 10 mg/kg/q8H. However, the patient became hypoxic and required oxygen at 4 L/min via a nasal cannula. Clinical examination revealed bilateral fine crepitations. Chest radiography, which showed bilateral non-homogeneous opacities, and laboratory investigations were suggestive of viral pneumonia, although we could not obtain a respiratory specimen for viral PCR. We initially started empirical antibiotics, suspecting hospital-acquired pneumonia which were discontinued. Acyclovir was continued, and the hypoxia resolved after five days. Neurologically, the sensorium improved, and the patient became conscious and well-oriented; however, the rigidity persisted. At this point, the patient developed urinary retention followed by painless frank haematuria. Abdominal ultrasonography suggested cystitis with bladder clots. As the patient had no history of catheterisation or urological intervention and there was no evidence of infection or bleeding diathesis, the possibility of varicella zoster-induced haemorrhagic cystitis was considered. The haematuria resolved with supportive care. He received acyclovir for 14 days, followed by valacyclovir 1000 mg twice daily for 7 days.

Seven months post-illness, our patient still has residual symptoms in the form of minimal rigidity; however, the patient has no residual cutaneous or respiratory symptoms.

3. Discussion

The reactivation of varicella zoster following SARS-CoV-2 vaccination has been increasingly reported, with mRNA vaccines being the most frequently implicated, followed by viral vector vaccines [2,3]. Cutaneous and ocular manifestations have been described; however few reports on meningitis and other systemic manifestations have been published [4]. A systematic review reported that the median duration from vaccination to onset of symptoms to be 10 days [4].While reactivation has been found to occur after both the booster and first doses, one study postulated that the risk of zoster reactivation is higher after the first dose [5].

We conducted a PubMed, EMBASE, and SCOPUS search using the keywords “zoster encephalitis”, “zoster meningitis”, “SARS-CoV-2 vaccine” and “varicella zoster” and found 11 reports of zoster meningitis cases following SARS-CoV-2 vaccination in the literature [6–13]. There was significant heterogeneity in the time taken for the symptoms to manifest after vaccination, with durations ranging from five to forty-one days. We also noted that the reactivation itself was not dose dependent, with six cases occurring after the first dose of the vaccine, one after the second, and one after a booster dose. In the remaining three patients, the dose was not specified. While the majority of cases occurred after mRNA vaccines, we noted three cases following the ChAdOx1 nCoV-19 (AZD1222) vaccine.

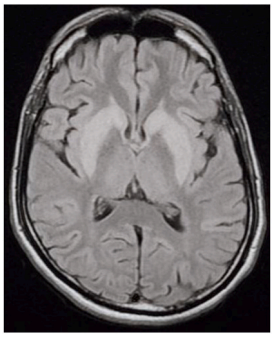

Fig. 1. Axial T2 FLAIR MRI image showing bilateral hyperintensity of caudate and lentiform nuclei.

Of these, two were above the age of 60 years, while the third patient had an underlying diagnosis of chronic hepatitis B. All three patients presented with meningitis alone and showed complete resolution of symptoms, with no residual deficits.

Several explanations have been proposed for this phenomenon. Cell-mediated immunity forms the backbone of the immune response to both SARS-CoV-2 infection and vaccination. Robust quantitative and qualitative T cell responses are more likely to be correlated with reduced disease severity and a reduced incidence of active infection following vaccination than just the humoral response [14]. A strong vaccine-induced T cell response causing a shift in naïve CD4 and CD8 cells, leaving the varicella zoster specific CD4 and CD8 cells unable to control the latent disease, is one of the major mechanisms proposed to explain the reactivation of varicella zoster post SARS-CoV-2 vaccination [15]. Other factors include vaccine-induced transient lymphopenia, alteration of toll-like receptor signalling, triggering of a pro-inflammatory cytokine cascade, and immunosenescence secondary to advancing age [5,16,17].

The activation of the pro-inflammatory cascade in response to the S protein, which is otherwise known as the 'spike hypothesis' is more marked in mRNA vaccines. This hypothesis along with the immunogenicity of the lipid nanoparticles used in the mRNA vaccines could explain the more severe manifestations of zoster noted with mRNA vaccines [18,19]. However, it is important to recognize that vector vaccines can cause similar manifestations, which can be attributed to any of the mechanisms causing adverse effects, such as T cell activation, stimulating Type 1 interferon production, shorter spike protein variant production, to name a few [20].

Despite receiving the appropriate therapy, the patient continued to develop complications during the course of treatment. One possibility for this is severe disease-causing T cell exhaustion, as demonstrated by his significantly low CD3,4 cell count during the illness, which is one of the mechanisms hypothesized in severe COVID as well. Therefore, antiviral therapy was administered for a prolonged period of 21 days.

4. Conclusion

This case highlights the importance of considering varicella zoster reactivation in a patient presenting with encephalitis or pneumonia post SARS-CoV-2 vaccination, especially considering the mortality and morbidity associated with these manifestations, if not promptly treated. We would also like to underscore the fact that approximately 90 % of varicella zoster reactivations post SARS-CoV-2 vaccination are not medically serious complications as per the current evidence [4] and should therefore, not be considered as an obstacle to either getting vaccinated or continuing with the vaccination schedule even if herpes zoster is observed to manifest after an initial dose.

Ethics statement

The patient provided informed consent for the publication of their anonymised case details and images. R. Gopi, W. Stanley, S. Surkunda, S. Rajagopal report no conflicts of interest or funding to declare.

Data availability

The data has been included in the article.

CRediT authorship contribution statement

Ranitha Gopi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Weena Stanley:** Data curation, Investigation, Methodology, Supervision, Validation. **Shashikala Taggarshe Surkunda:** Data curation, Investigation, Methodology, Supervision, Validation. **Sriraam Rajagopal:** Data curation, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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