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# Aseptic meningitis following AZD1222 COVID-19 vaccination

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## ABSTRACT

The AZD1222 is one of the vaccines used against coronavirus disease 2019 (COVID-19), which is currently being used in many countries worldwide. Some important neurological side effects have been reported in association with this vaccine, but aseptic meningitis has not yet been reported. Herein, we report a case of aseptic meningitis in a 26-year-old health care worker, following the first dose of the AZD1222 vaccine.

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## 1. Introduction

COVID-19 vaccination has been proven to reduce the risk of serious illness and death [1]. Although the safety of vaccines is monitored during clinical trials, some rare side effects might not be identified until they are used for vaccination of the general population. In phase 2 and 3 of the AZD1222 COVID-19 vaccine trials, good immunogenicity was reported, and no serious side effects were seen with the vaccine [2].

Aseptic meningitis is defined as meningeal inflammation and pleocytosis ( $\geq 5$  cells/mm<sup>3</sup>) of cerebrospinal fluid (CSF) in the absence of infection [3]. It is usually self-limited and resolves within a week [4]. Aseptic meningitis has previously been reported with mumps, varicella, and influenza vaccines [5–7], but data regarding its incidence with COVID-19 vaccination is scarce. There is one report of aseptic meningitis following the BNT162b2 mRNA vaccine [8].

Herein, we report a case of aseptic meningitis following the AZD1222 vaccine.

## 2. Case presentation

A 26-year-old otherwise healthy female healthcare worker, with no family history of autoimmune diseases, received the first dose of AZD1222 vaccine on April 20th, 2021. She developed low-grade fever a few hours after receiving the shot, which was followed by a frontal tension type headache, and photophobia the next morning. There was

no neck stiffness in physical examination; Kernig and Brudzinski signs were negative, and the optic disc appeared normal. No cranial nerve involvement was detected during the physical examination. She was put on acetaminophen (500 mg TDS), and Ibuprofen (400 mg BID) for symptom relief. After two days, the symptoms did not resolve and the headache worsened. The patient reported her pain score as 8 out of 10, along with nausea, vomiting, and myalgia. Results of two polymerase chain reaction (PCR) tests for Covid-19 were negative. Blood test results revealed unremarkable complete blood count (CBC) with normal neutrophil and lymphocytic count, normal hemoglobin, and slightly increased platelet count (510,000/mm<sup>3</sup>); and markers of inflammation, erythrocyte sedimentation rate, and C-reactive protein, reported normal. Intravenous fluids and ketorolac were administered which resulted in some relief of symptoms for 4 h. After that, the symptoms recurred and the patient reported a severe headache with the pain scored as 9 out of 10. With worsening headache and photophobia, magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and magnetic resonance venography (MRV) of the brain were requested and all three studies were normal. A computed tomography (CT) scan of the chest, was performed six days after the first symptoms and showed no sign of Covid-19 infection. At this stage, a lumbar puncture was performed, which showed 5 lymphocytes/mm<sup>3</sup> in the cerebrospinal fluid (CSF) and slightly increased protein (54 mg/dl). The CSF/serum glucose ratio was 0.7. The result of the CSF viral panel was negative. The titer of serum antinuclear antibody was normal at 1/80. The patient was diagnosed with aseptic meningitis and was put on prednisolone 20 mg daily, for three days, which then was tapered during the next 9 days. Shortly after treatment, the headache fully resolved and the patient remained symptom-free. Three months later, she received the second dose of the vaccine and just had some mild constitutional symptoms which resolved spontaneously in three days.

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### 3. Discussion

We reported a case of severe headache after receiving the first dose of the AZD1222 vaccine. All workups were negative and with the CSF evaluation, the diagnosis of vaccine-associated aseptic meningitis was made.

Vaccines appear to be safe and life-saving. There have been reports of some serious neurologic adverse effects, such as demyelinating syndromes associated with the administration of viral vaccines in the past; but epidemiological studies have revealed no increased risk of these adverse effects with vaccination [9]. AZD1222 vaccine is among many COVID-19 vaccines currently being used around the world. Although phase 2/3 of its clinical trial found no serious adverse effects with vaccine administration, some serious adverse effects have been reported. Hematologic adverse effects of AZD1222 include cerebral venous thrombosis [10], and vaccine-induced thrombotic thrombocytopenia (VITT) [11]. Some serious neurologic adverse effects have also been reported which include Guillain Barre Syndrome [12], and acute transverse myelitis [13].

Aseptic meningitis is a term including all causes of meningeal inflammation with negative CSF cultures. It has a mild course and resolves spontaneously during a week [4]. Viruses are the most common cause of infectious aseptic meningitis. Non-infectious etiologies include neoplastic and drug-induced etiologies (most commonly reported with non-steroidal anti-inflammatory drugs), as well as meningeal involvement in connective tissue diseases (e.g. systemic lupus erythematosus) [14]. Also, aseptic meningitis has been reported following certain vaccines such as measles, mumps, and rubella vaccine [15], varicella-zoster vaccine, yellow fever vaccine, rabies vaccine, pertussis vaccine, and influenza vaccine [6,7].

There has been no report of aseptic meningitis with the AZD1222 vaccine yet. Regarding COVID-19 vaccines, there is one recent report of COVID-19 mRNA vaccine causing aseptic meningitis [8]. The true mechanism by which vaccines cause aseptic meningitis is unknown. The AZD1222 is a viral vector vaccine based on the chimpanzee adenovirus Y25 (ChAdOx1). To make immunity, vaccines interact with the immune system; which leads to the expression of the pro-inflammatory cytokines (Interleukin-1, Interleukin –6, Tumor Necrosis Factor- $\alpha$ , and prostaglandins); then the innate immune system starts a series of events that cause inflammation, as well as the immunity to the pathogen, by stimulating the memory cell production. The mediators involved in the immune response to the vaccine might affect other body systems such as the neural system [16]. Based on the genetic background and the memory of the immune system, this neuroinflammation could be seen in a spectrum from mild (as in aseptic meningitis) to severe (causing neurologic involvement and autoimmunity). A report of the autopsy of 13 COVID-19-related deaths, revealed microvessel involvement in brain vasculature, with endothelial cells having the COVID-19 spike protein. In the mice brain, the S1 spike subunit was co-localized with inflammatory cytokines. It was shown that the S1 subunit can cause endothelial damage in microvessels via cytokine expression and complement activation [17]. As coronaviruses are known to have neurotropic features [18], it is probable that the vaccines against them, which present the same viral spike proteins, cause the same neurologic side effects as the viruses cause themselves. There are some possible mechanisms by which coronaviruses might affect the central nervous system. The presence of viral proteins and genetic material in CSF and brain tissue [19], and immune-mediated mechanisms are among the proposed mechanisms [20,21].

One important side effect of the AZD1222 vaccine is vaccine-induced thrombotic thrombocytopenia (VITT) [11]. The most important matter in managing this patient was ruling out VITT. This way, the patient was screened and followed for this important side effect via imaging studies, CBC, and D-dimer, all of which showed no finding in favor of VITT. According to the self-limited course of aseptic meningitis, the COVID-19 vaccination should not be postponed because of it. However, it is important to rule out critical side effects of vaccines such as VITT and

cerebral venous thrombosis before labeling the diagnosis of aseptic meningitis.

The other case of aseptic meningitis with mRNA Covid-19 vaccine was a female patient who experienced symptom relief after receiving intravenous methylprednisolone [8]. In our case, the symptom relief occurred shortly after the administration of prednisolone. Although the exact mechanism of meningeal inflammation following vaccination is unclear, these two cases suggest an immune-mediated mechanism for vaccine-induced aseptic meningitis. It might be helpful to monitor these patients for autoimmune diseases in the future.

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### CRedit authorship contribution statement

**Arefeh Zavari:** Writing – original draft. **Negin Mahmoudi Hamidabad:** Writing – review & editing, Conceptualization, Writing – original draft. **Morteza Hassanzadeh:** Conceptualization, Writing – review & editing.

### Declaration of Competing Interest

The authors declare no conflict of interests.

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