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Meningitis after COVID-19 vaccination, a systematic review of case reports and case series

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Abstract

Introduction Vaccination is considered as one of the most promising strategies to overcome the COVID-19 pandemic. However, it could be associated with rare but serious complications. In the present study, we aimed to review the clinical course and etiology of post COVID-19 vaccination meningitis.

Methods After a systematic search in PubMed, Scopus, and Web of Sciences online databases as well as Google Scholar, documents were screened and qualified. Then data extraction was performed and the most frequent underlying agent of meningitis was found based on the reported cases.

Results Overall, 35 cases of post COVID-19 vaccination meningitis from 33 articles were included in the review. Among them, 12 cases had proven viral diagnosis and 23 of them were reported to be vaccine-induced. The most frequent viral pathogen among the cases was VZV. The most prevalent symptom was headache, and the most common time of appearance symptoms was one week after vaccination.

Conclusion Overall, our study suggested meningitis as a critical but not devastating complication of COVID-19 vaccination. Almost all patients responded well to common agents used to manage viral or vaccine-induced meningitis. It is recommended to monitor patients with a history of chickenpox after COVID-19 vaccination regarding the development of meningitis.

Keywords COVID-19, Vaccine, Meningitis

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Introduction

Vaccination is considered as one of the most promising strategies to overcome the COVID-19 pandemic. Currently, four major types of vaccines are being used including COVID-19 viral vector-based vaccines, mRNA-based vaccines, protein-based vaccines, and attenuated or inactivated virus vaccines. Viral vector-based vaccines, use adenovirus to deliver a specific sequence of SARS-CoV-2 genome to human cells. Human cells produce SARS-CoV-2 spike protein according to this genetic material. Consequently, the immune system starts a defensive response following exposure to this protein.



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The mRNA-based vaccines introduce SARS-COV-2 RNA to human cells which produce SARS-COV-2-specific protein from this genetic messenger. This protein triggers the immune system to run a defensive reaction. In addition, inactivated or attenuated vaccines, cause immunogenicity using killed or attenuated SARS-COV-2 virus. Also, protein-based vaccines directly expose human cells to fragments of or whole spike protein to incite an immune response. Different countries gave emergency approvals to these vaccines for human use, in the COVID-19 era [1]. According to the latest World Health Organization (WHO) report, a total of 5,548,001,227 people around the world received at least one dose of COVID-19 vaccination [2].

Several neurological complications have been attributed to COVID-19 [3–6] and it has been reported to potentially change the pattern of neurological disorders like stroke [7, 8]. However, there is also a risk of developing several serious neurological complications following COVID-19 vaccination including acute disseminated encephalomyelitis, transverse myelitis, Guillain-Barré syndrome, aseptic meningitis, myositis macrophagic, and myofasciitis [9–11]. Several pathophysiological mechanisms, like direct neurotoxicity, aberrant immune reactions, and molecular mimicry have been suggested to explain these complications after vaccination [12]. Several neurological conditions affecting the brain, spinal cord as well as cranial and peripheral nerves are described after COVID-19 vaccination [13]. One of the rare but serious complications following vaccination for COVID-19 is meningitis [14]. Classically, meningitis is characterized by some combination of fever, neck stiffness, headache, and altered mental status as well as photophobia, nausea, and vomiting [15, 16]. Meningitis may be caused by bacteria (e.g. *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Mycobacterium tuberculosis*) [17], fungi (predominantly *Cryptococcus neoformans*), parasites (e.g., *Cysticercosis due to Taenia solium*), viruses (Non-polio human enteroviruses (NPEV), Herpes simplex viruses (HSV), and varicella zoster virus (VZV)) [18, 19], or may have noninfectious etiologies such as rheumatologic conditions, malignancies or pharmacological agents [16, 20]. This study aims to review all cases of developed meningitis following COVID-19 vaccination.

Material and methods

Study design

This systematic review was conducted in accordance with the PRISMA 2020 guidelines. It aims to review cases of meningitis developed following COVID-19 vaccination and perform an in-silico analysis to design a vaccine for the common underlying agent. The review protocol is registered in PROSPERO (CRD42023414137).

Eligibility criteria

Studies were included if they reported cases of meningitis, arachnoiditis, choriomeningitis, or meningoencephalitis associated with COVID-19 vaccination. Articles were excluded if they provided insufficient clinical information, were not published in English, or were not peer-reviewed. Case reports, case series, and observational studies were eligible for inclusion.

Information sources and search strategy

A comprehensive literature search was conducted across four databases: ISI, PubMed, Scopus, and Google Scholar. The search included studies published up to September 5, 2024, without language restrictions. The search terms used were combinations of keywords such as “COVID-19 Vaccines,” “arachnoiditis,” “meningitis,” “choriomeningitis,” and “meningoencephalitis.” A detailed search strategy for each database is provided in the supplementary material.

Study selection process

All identified records were imported into EndNote X8 software, where duplicates were automatically removed. Two independent reviewers screened the titles and abstracts of the remaining studies against the eligibility criteria. Full-text screening was then performed to confirm eligibility. Disagreements between reviewers were resolved through discussion or by consulting a third reviewer when necessary. A PRISMA flow diagram summarizing the selection process is provided in the results section.

Data collection process

In the current study, the data of cases in which evidence of an underlying microorganism was found, were presented in the “viral meningitis” section and for whom without any evidence of an underlying organism is presented in the “vaccine induced meningitis” section. Data extraction was performed independently by four authors using a predefined checklist that included details on authorship, year of publication, number of cases, patient comorbidities, clinical symptoms, vaccine characteristics, clinical course, and outcomes. Any discrepancies in data extraction were discussed and resolved by the group.

Data items

The primary data items extracted were related to clinical presentation, vaccine type, and disease outcomes. Additional variables included demographic data, comorbidities, time of the presentation, and follow-up information. In the case of having missing data that part is demonstrated by “-” in the tables.

Quality assessment

The quality of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools for case reports and case series. These tools assess the methodological quality across eight domains for case reports [21] and ten domains for case series [22]. Quality assessment was performed independently by two reviewers, and disagreements were resolved by discussion.

Results

Study characteristics

The systematic search identified 448 records, of which 385 remained after the removal of 63 duplicates. In total, 348 records were excluded after screening the titles/abstracts. After assessing the 37 articles for eligibility, 4 studies were excluded due to insufficient clinical information from the disease course. Finally, 33 articles met the eligibility criteria and were reviewed in the present study (Fig. 1).

Patients demographic and clinical characteristics

Overall, thirty-five patients with meningitis following COVID-19 vaccination were included in the review, from 27 case reports and six case series. Investigation of participant characteristics showed that 45.7% ($n=16$) of patients were male and 54.2% ($n=19$) of them were under 40 years old. Among the vaccine types, mRNA technology vaccinated 77.1% ($n=27$) of participants, and about 17.1% ($n=6$), and 2.8% ($n=1$) were vaccinated by viral vector, and inactivated vaccine, respectively. Therefore, it can be stated that most of the patients used mRNA-based vaccines. Also, among the participants, only three patients had a positive COVID test by PCR after vaccination, so it can be claimed that complications and manifestations are probably related to vaccines. Vaccine-induced meningitis constituted 65.7% ($n=23$) of the patients. Also, 34.3% ($n=12$) of the included patients had viral meningitis after COVID-19 vaccination. Among all patients, four had dyslipidemia (11.4%), four had migraine (11.4%) and

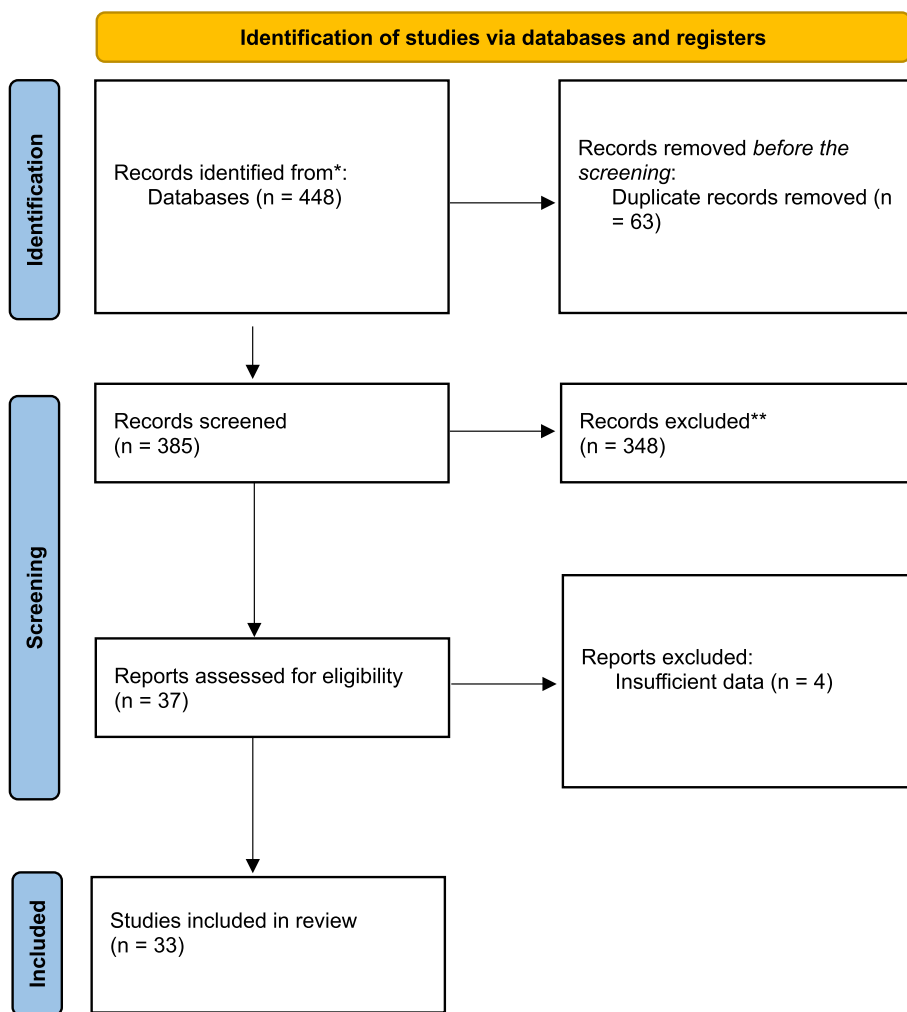


Fig. 1 Prisma flow chart

12 (34.2%) of them didn't have a remarkable past medical history. Imaging didn't have major therapeutic benefits in most of the patients.

Vaccine-induced meningitis

Clinical and paraclinical examination of patients with vaccine-induced meningitis revealed that among the 23 patients, 73.9% ($n=17$) and 21.7% ($n=5$) were vaccinated by mRNA and viral vector, respectively. The most prevalent clinical symptom in aseptic patients was a headache at 86.9% ($n=20$). After that, fever ($n=14$) and nausea ($n=6$), were 60.8 and 26.0% respectively. Neck stiffness was detected in five (21.7%) patients. Also, the time interval between the vaccine and the appearance of these symptoms included four periods. In 12 (52.1%) patients symptoms appeared after the first dose, in 9 (39.1%) of them after the second dose, and in one (4.3%) of them after the third dose of vaccination. The symptoms of the two patients appeared a few hours after vaccination.

Most patients' symptoms appeared within one week (39.1%) after vaccination. After that, two weeks and three weeks were 30.5%, and 30.5% respectively. The main laboratory findings among aseptic patients are shown in Table 1. Most of the studies, reported methyl prednisone, Dexamethasone, and NSAIDs as the major therapeutic regimens for aseptic meningitis. Symptoms were fully resolved in 13 (56.5%) patients whereas at least three (13.0%) of them maintained symptomatic after one month of follow-up Table 1.

Viral meningitis

Clinical and paraclinical examination of 12 patients with viral meningitis revealed that Pfizer vaccinated 83.3% ($n=10$) of patients among nine and about 16.6% ($n=2$) were immunized by AstraZeneca. In 10 out of the 12 patients, varicella zoster virus (VZV) was suggested to be the causative microorganism for meningitis. In one other [45], a CSF cytomegalovirus (CMV) PCR was positive, but the patient had no clinical evidence for ocular or systemic CMV. In the last one, no viral cause could be determined [21]. These two cases responded well to antiviral therapy. The most prevalent clinical symptom in patients with viral etiology was a severe headache in almost all patients, followed by fever, vesicular rashes, and nausea were 58.3, 50, and 33.3%, respectively. The main dermatome affected by vesicular rash was T10. Neck stiffness and photophobia were detected in four (33.3%) and three patients (25.0%). Also, the time interval between the vaccine and the appearance of symptoms mostly appeared within one week (58.8%) after vaccination, followed by two weeks, one day, and more than three weeks 16.16, and 16%, respectively. In eight (66.6%) patients symptoms appeared after the first dose and in three of them (25%)

appeared after the second dose. A history of chickenpox was noted by five (41.6%) patients and none of them were vaccinated for varicella zoster.

The main laboratory findings among these patients were increased CSF protein levels, CRP, and pleocytosis in 8 (66.6%) (mostly lymphocytic), 3 (25%), and 12 (100%) of them. In most of the studies, intravenous (500-300 mg) and oral (1500-4000 mg) acyclovir (2–21 days) was the first-line therapeutic agent for viral meningitis. Almost, full recovery was achieved in nine (75%) of the patients Table 2.

Eventually, the results of the study determined that in vaccine-induced and viral meningitis, the most used vaccine was Pfizer, the most prevalent symptom was headache, and the most common time of appearance symptoms was one week after vaccination.

Quality assessment

Among case reports, five received the highest score (8/8, 18.5%) and one received the lowest score (4/8, 3.7%). The overall mean score of the studies was 6.7. Reporting patients' demographic information and clear history were the most fulfilled criteria (100%, 96.2%). The least fulfilled criteria were describing adverse events after therapy (33.4%) as shown in Table 3. Among case series, two of them received a score of 9/10, and one received a score of 1/8. The latter one was a report of a series of cases in the form of a letter to the editor. The mean score of the case series was 7/8. The most fulfilled criteria were the consecutive inclusion of the patients (100%), whereas the least was describing clear inclusion criteria (50%) as shown in Table 4.

Discussion

The term "meningitis" refers to the inflammation of the meninges which surround the brain and spinal cord. Its association with mumps, measles, and rubella vaccination has been extensively documented [22, 57]. However, in the wake of the COVID-19 pandemic, there has been a notable increase in the utilization of various available vaccines to mitigate the adverse effects of COVID-19. Some published studies have reported reactions and side effects associated with these vaccines, which were initially developed as prophylactic measures against the severe and fatal consequences of the virus [45, 58]. For instance, the BNT162b2 mRNA COVID-19 vaccine has been linked to cases of aseptic meningitis among many recipients [59]. Our comprehensive search for performing a systematic review of meningitis after COVID-19 vaccinations revealed some essential information about meningitis cases due to the COVID-19 vaccines. Our study showed that most participants received Pfizer (65.6%), which greatly impacted the incidence of

Table 1 Drug-induced meningitis

ID (Ref)	Author (Year)	Study type, country	Sex (Age)	PMH/ Comorbidity	Symptoms/ physical examination	Vaccine type, dosage	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
2, [23]	Senda (2022)	Case report, Japan	F (72)	Rheumatoid vasculitis, diabetes mellitus, and hyperlipidemia (Daily prednisolone 6 mg)	General fatigue and headache / Depressed level of consciousness (GCS=9)	mRNA, first	Serum: slightly increased D-dimer CSF WBC=4 cells/mm ³ CSF Prot=173.2 MG/DL	3 days	MRI: high signals at the surface of the cerebral cortex especially and in the white matter of the bilateral frontotemporal areas on diffusion-weighted imaging (DWI), with signals being particularly strong on the right side compared with the left side FLAIR: abnormal signal in both the cerebral gray and white matter and diffuse cerebral cortex swelling in the bilateral frontotemporal areas	Intravenous immunoglobulin and methylprednisolone	Two months later: MRI disappearance of high signals at the surface of the cerebral cortex and white matter on DWI and improvements in the abnormal signals in the cerebral gray and white matter as well as diffuse cerebral cortex swelling on FLAIR images	Negative
6, [24]	Cameiro (2022)	Case report, Portugal	F (62)	Anxiety and dyslipidemia	Mild headache, difficulties concentrating, fatigue, dizziness, myalgia, and unstable gait, all worsened in orthostatism / symptomatic postural tachycardia without changes in blood pressure	mRNA, first	Blood = mild lymphopenia CSF WBC = 301 cells/mm ³ CSF OP = 8 cm H ₂ O CSF Prot = 208 mg/dl CSF Virus PCR = -	1 day	MRI = unremarkable	IV Dexamethasone 5 mg	Complete clinical improvement the following day after starting medication	Negative
7, [25]	Fernandes (2022)	Case series, Trinidad and Tobago	F (61)	Verrucous hyperplasia	headache, fever, diplopia, urinary retention, Neck stiffness, ophthalmological examination: diplopia to extreme lateral gaze bilaterally, paresthesias of the thighs and calves bilaterally, and ataxia	Viral vector, first	Normal CBC, LFT, and CRP CSF WBC = 200 (lymph pred) CSF prot = 65 mg/dL	18 days	MRI brain revealed non-enhancing, non-specific deep white matter lesions but all other investigations were normal	IV Dexamethasone	The patient's headache, fever, and diplopia resolved four days later. Ataxia and diplopia resolved two months later	Negative

Table 1 (continued)

ID (Ref)	Author (Year)	Study type, country	Sex (Age)	PMH/ Comorbidity	Symptoms/ physical examination	Vaccine type, dosage	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
8, [26]	Ghang (2022)	Case series (letter), Korea	F (in her twenties)	-	headache and intermittent fever for 20 days (38.5 °C), necrotizing cervical lymphadenitis, and hair loss	mRNA, first	ESR 120 mm/h CRP = 4.3 mg/dl CSF Pathogens = -	10 days		Oral prednisolone 15 mg and Naproxen 500 mg BID	This patient had low disease activity and was followed up for approximately 7 months	Negative
11, [27]	Kang (2022)	Case report, Korea	M (32)		headache for 1 week (stabbing pain in the back), chills, nausea, general weakness, and dizziness	mRNA, second	Serum CRP = 0.03 mg/dL CSF WBC = 480 cells/mm ³ (lymph pred) CSF Prot = elevated CSF glucose = NL	2 Weeks	Brain MRI (with and without contrast) = Normal	Methylprednisolone (500 mg/day)	Completely asymptomatic two months after	Negative
13, [28]	Lee (2022)	Case report, Korea	M (18)	-	generalized and recurring headache (the headache was relieved on sitting and aggravated on lying down), nausea, febrile sense, and chills	mRNA, second		3 weeks	Brain MRI = subtle leptomeningeal enhancement along both cerebral convexity on the fluid-attenuated inversion recovery sequence	Serum CRP = 0.74 CSF WBC = 115 cells/dL CSF RBC = 180/uL CSF glucose = 65 mg/dL CSF Prot = 67.2 mg/dL	Full recovery at HD5	Negative

Table 1 (continued)

ID (Ref)	Author (Year)	Study type, country	Sex (Age)	PMH/ Comorbidity	Symptoms/ physical examination	Vaccine type, dosage	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
16, [29]	Jeanin (2022)	Case report, France	F (35)	Unremarkable	Headaches, abdominal pain, nausea	Viral vector, First		1 Week	Brain MRI at week 4 showed white matter hypersignals of the area postrema, the cerebral peduncle and the left thalamus. Brain imaging found new lesions of the corpus callosum, the right optic radiation, the pons, and the subcortical frontal left white matter, without gadolinium enhancement. It also revealed evidence of intracranial hemorrhage (ICH), with enlarged optic nerve sheaths, lateral sinus stenosis, and empty sella syndrome. An asymmetric papilledema with normal visual acuity was found upon ophthalmological examination. A new MRI identified a right optic neuritis with bilateral optic perineuritis. Spinal cord MRI identified a 10 mm cervical lesion		Five months after the onset of symptoms, an MRI found regression of the inflammatory lesions and ICH signs, and disappearance of the medullar lesion without atrophy. There was no papilledema or visual field defect. Six months after the onset of symptoms, the patient presented decreased visual acuity at 9/10th and headaches despite increased acetazolamide doses	Negative

Table 1 (continued)

ID (Ref)	Author (Year)	Study type, country	Sex (Age)	PMH/ Comorbidity	Symptoms/ physical examination	Vaccine type, dosage	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
17, [30]	Ganapathiram (2022)	Case report, United Kingdom	F (22)		Headache, vomiting, neck pain, diarrhea, photophobia, abdominal pain, and malaise, fever over 40 °C, tachycardia, Rapid, progressive multiorgan failure happened over the next 18 h, resulted in hypoxia (respiratory), hypotension (cardiovascular), azotemia with oliguria (renal), nonabsorption of feeds, and diarrhea (GI)	mRNA, second	Blood WBC = 15,100 Blood CRP = 349 mg/L CSF prot, WBC = NL Severe hypoxia, lactic acidemia, and hypotension which was unresponsive to IV fluids	2 days	Brain CT = NL	2 gm/kg of IV immunoglobulin and 1 gm of methylprednisolone daily for 5 days	Full recovery at HD13	Negative
18, [31]	Torreallba-Acosta (2021)	Case report, USA	M (77)	Coronary artery disease, hyperlipidemia, and hypothyroidism	Headache, confusion, fever generalised rash (non-viral), dizziness and double vision	mRNA, first	CSF WBC = 120 cells/mm ³ CSF glucose = 65 mg/dL CSF Prot = 124 mg/dL All CSF cultures were negative	1 day	Brain and cervical MRI = NL	4-day course of 1 g methylprednisolone once a day	The patient progressively improved, achieving his baseline before the fourth dose of methylprednisolone	Negative

Table 1 (continued)

ID (Ref)	Author (Year)	Study type, country	Sex (Age)	PMH/ Comorbidity	Symptoms/ physical examination	Vaccine type, dosage	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
19, [32]	Gogu (2022)	Case report, Romania	M (55)	Diabetes mellitus	Severe headache, mixed aphasia, right hemiparesis, agitation, and incomplete left ophthalmoplegia, without fever	Viral vector, -	Serum CRP= 19.8 mg/L CSF WBC and RBC = 0 CSF Prot= 62 mg/dL	9 days	Brain CT: hyperattenuation of the left cavernous sinus and left lateral sinus (concerning for sinus thrombosis) MRI of the brain with and without contrast in addition to brain magnetic resonance angiography (MRA)/magnetic resonance venography (MRV): The presence of thrombus in the cavernous sinus was refuted by cerebral MRA/MRV. Also, findings were suggestive of Tolosa-Hunt syndrome. Non-contrast brain CT showed left capsulolenticular and temporal hypodensities. The appearance was suggestive of encephalitis	One gram of IV. Methylprednisolone for three days	The patient died (probably on HD 8)	Positive
20, [33]	Sumi (2022)	Case report, Japan	M (55)	stage IV non-small cell lung cancer	Fever, disorientation	mRNA, third	Serum CRP= 17.22 mg/L	1 day	Brain MRI showed meningitis in the parietal region	Steroid pulse therapy		
21, [34]	Tagini (2022)	Case report, Switzerland	F (in her late twenties)	Polycystic ovary syndrome	Unusual bi-temporal, retro-orbital headaches, malaise, fever, multiple painful genital and oral ulcers, and pseudofolliculitis / bilateral papillary edema	mRNA, second	CSF OP = 27 cm H2O Mild lymphocytic pleocytosis and slight elevation of CSF proteins	15 days	Cerebral MRI showed intracranial hypertension	Prednisone 1 mg/kg/day	At the 1.5-month follow-up visit, the mucocutaneous lesions had completely healed. However, the patients still complain of retro-orbital pain, associated with eyestrain	-
22, [35]	Saito (2021)	Case report, Japan	F (42)	Migraine	Severe headache, fever, nausea, and jolt accentuation	mRNA, first	Serum CRP= 9.85 mg/dL CSF OP = 22 cm H2O CSF WBC = 528 cells/mm ³ CSF Prot = 35.7 mg/dL	1 week	MRI (with and without contrast): NL	Five days of intravenous methylprednisolone (500 mg/day)	Discharge on HD 7 Never noticed headache, nausea, and fever at least 4 months post-discharge	Negative

Table 1 (continued)

ID (Ref)	Author (Year)	Study type, country	Sex (Age)	PMH/ Comorbidity	Symptoms/ physical examination	Vaccine type, dosage	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
23, [36]	Bogs (2022)	Case report, Germany	M (15)		Headache, neck rigidity, positive Brudzinski and Kernig signs together with fever of 38.8 °C and nausea, vitreous floaters / Oral aphthous ulcers (lips, tongue, and inner cheeks)/ slight maculopapular exanthema on his cheeks, a few erythema nodosum-like lesions and a single pustular lesion on his lower legs as well as swelling of his right knee,	mRNA, second dose	Serum CRP= 5.34 mg/dL CSF prot = 69.4 mg/dL CSF glucose = 65 mg/dL	10 days	Cranial MRI with a gadobutrol-enhanced T1-weighted fast field echo (T1-FFE) sequence performed three days after the lumbar puncture showed slight patchy- and leptomeningeal enhancement. Minimal inhomogeneities in the posterior vitreous detected by OCT	-	Remained asymptomatic for the following two months	Negative
26, [37]	Dupon (2022)	Case report, Belgium	F (34)		severe pan cranial headache, fever, diffuse myalgia, photo- and photophobia, neck rigidity as well as progressive symmetric and inflammatory joint pain in both wrists, ankles, and knees	mRNA, second dose	Serum CRP= 169 mg/L CSF WBC = 188 cells/mm ³ (lymph pred)	6-8 h	Normal brain CT scan and MRI	high-dose oral methylprednisolone scheme	-	-

Table 1 (continued)

ID (Ref)	Author (Year)	Study type, country	Sex (Age)	PMH/ Comorbidity	Symptoms/ physical examination	Vaccine type, dosage	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
29, [38]	Chan (2022)	Case series, Singapore	F (43)	Uterine fibroids	Severe headache, myalgia, fever, and generalized papular rashes over her trunk, back, lower and upper limbs	mRNA, second dose	Serum CRP= 162 mg/L Serum ESR= 54 mm/h CSF OP= 22 cmH2O CSF WBC 265 cells/ul Infective PCR panel (INCLUDING VZV) = negative CSF prot= 96 mg/dL	4 days	Brain MRI= NL	She was managed initially as for infectious meningitis with ceftriaxone and acyclovir. Antimicrobials were subsequently stopped, and the patient was managed with non-steroidal anti-inflammatory drugs (NSAIDs)	Her symptoms of fever, myalgia and rashes completely resolved and her headache improved upon discharge. At follow-up one month later, she remained well and asymptomatic	Negative
30			F (38)	None	Headache, nausea, and neck pain	mRNA, first dose	CSF OP = 17cmH2O Viral panel= - CSF WBC = 340 cells/ul (lymph pred) CSF Prot = 74 mg/dL	10 days	MRI showed a tiny 0.4 cm enhancing linear focus seen in the right hemipons with faint T2W/FLAIR hyperintensity suggestive of capillary telangiectasia, with otherwise no abnormal parenchymal or leptomeningeal enhancement	NSAIDs	The patient remained well and asymptomatic at a one-month follow-up	Negative
31, [39]	Zavari (2022)	Case report, Iran	F (26)	None	Frontal tension-type headache, fever, photophobia, nausea, vomiting, and myalgia	Viral vector, first dose	Serum CRP=NL CSF WBC = 5 cells/mm3 (lymph pred) CSF prot = 54 mg/dL CSF viral panel = -	A few hours later	MRI, MRA, and MRV of the brain were normal	Acetaminophen (500 mg TDS), and Ibuprofen (400 mg BID) for symptom relief, Prednisolone 20 mg daily	Shortly after treatment, all symptoms were relieved. Three months later, she received the second dose of the vaccine and just had some mild constitutional symptoms which resolved spontaneously in three days	Negative
33, [40]	Chen (2023)	Case series, Taiwan	M (57)	Schizophrenia	Seizure	mRNA, first dose	CSF OP = 11 cm CSF WBC < 5 cells/ul CSF prot = 67 mg/dL	19 days		Levetiracetam	No seizures recurred after discharge	-

Table 1 (continued)

ID (Ref)	Author (Year)	Study type, country	Sex (Age)	PMH/ Comorbidity	Symptoms/ physical examination	Vaccine type, dosage	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
34, [41]	Courssou (2022)	Case report, Japan	F (57)	None	Headaches and blurred vision / Ophthalmologic examination: bilateral and non-bilateral hypertensive granulomatous panuveitis, diffuse stromal edema with Descemet folds, bilateral conjunctival hyperemia, Tyndall effect with retro-desclerotic precipitates and posterior synechiae as well as Markedly thickening of choroid with both serous retinal detachment and choroidal folds	mRNA, first	Serum CRP= 14 mg/L CSF RBC= 1 cell/uL CSF WBC= 110 cells/uL (lymph pred) CSF prot= 28 mg/dL	3 weeks	Brain MRI= normal Initial OCT depicting a choroidal thickening with choroidal folds, both subsiding on control OCT after 4 days of treatment, making way for a small remaining serous retinal detachment	Mydriatic drops and peribulbar injections of dexamethasone 8 mg along with 3 intravenous pulses of methylprednisolone 15 mg/kg/day, further relayed by oral prednisone,	Three months after diagnosis, with prednisone 5 mg/day, the patient was asymptomatic with a bilateral visual acuity of 1.0	-
35, [42]	Kato (2023)	Case report, Japan	F (27)	Migraine without aura	Persistent bifrontal-throbbing headache that was more severe than her usual migraine attacks, photophobia / positive jolt accentuation without Neck stiffness, Kernig sign, and other neurological signs	mRNA, first	Serum WBC = 3450 cells/uL Serum CRP = 0.08 mg/dL Serum d-dimer = 0.97 ug/mL CSF cell count = 56 cells/mm ³ (100% mononuclear cells) CSF prot = 54 mg/DI CSF glucose = NL CSF OP = 30 cmH ₂ O Multiplex PCR for herpes virus DNA = negative	8 days	Normal MRI and brain CT scan as well as angiography and contrast enhanced CT venography (with and without contrast)	Six days of intravenous methylprednisolone (500 mg/day) 5 days after admission	The patient was discharged from the hospital on day 12 and remained well without severe headache at 1-month follow-up	SARSCoV-2 spike protein IgG = positive SARS-CoV-2 nucleocapsid protein IgG anti-body = negative

Table 1 (continued)

ID (Ref)	Author (Year)	Study type, country	Sex (Age)	PMH/ Comorbidity	Symptoms/ physical examination	Vaccine type, dosage	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
35, [43]	Kularathna (2024)	Case report, Sri Lanka	F (29)	Migraine/ the patients was diagnosed with Kikuchi disease complicated with aseptic meningitis	Headache, low grade fever, arthralgia, myalgia, loss of appetite, phonophobia, left axillary pain, no neck stiffness or focal neurological signs	Viral vector second	Serum WBC = 5310 cells/uL Serum CRP = 49.7 mg/L Serum anti-EBV IgM antibody = negative Serum Human Immunodeficiency virus 1 and 2 antibody = negative CSF cell count = 48 cells/uL (75% lymphocytes) CSF prot = 50.6 mg/dL CSF glucose = 2.5 mmol/L CSF Adenosine deaminase = negative Tuberculosis culture = negative	Two weeks	Abdominal ultrasonography = NL CT scan with contrast = axillary, para-aortic, and mesenteric lymphadenitis (necrotizing lymphadenitis in lymph node biopsy)	On day 38 of the illness, she was started on 45 mg of prednisolone daily. Two days after the commencement of steroids, she showed a good clinical response with reduction of the size of lymph nodes, settling of headache and fever	-	-
[44]	Ramesh, (2023)	Case report, Sri Lanka	69 (M)	Previously healthy/ the patient was diagnosed with aseptic meningitis complicated with cerebral salt wasting	Fever, generalized tonic-clonic seizures, severe myalgia, and arthralgia/ tachycardia (110 bpm) and prolonged capillary refilling time, normal neurological and ophthalmological examination	-, second	Serum WBC = 9240 cells/uL Serum CRP = 24 mg/dL Serum osmolality = 247 mosmol/L Urine osmolality = 121 mosmol/L Urine sodium = 186 mmol/L CSF cell count = 5 cells/uL (100% lymphocytes) CSF Glucose = 40 mmol CSF Prot = 38 mg/dL CSF culture no growth CSF Tuberculosis PCR = negative	Four days	Brain CT scan = NL	He was treated with initially hypertonic (3%) saline and followed by 0.9% saline. Also, we have started fludrocortisone 0.2 mg per day, fever was had been settled by Paracetamol	-	COVID-19 RT-PCR = negative

Prot Protein, CT scan Computed tomography, MRI Magnetic resonance imaging, CSF Cerebrospinal fluid, CRP C-reactive protein, OCT Optical coherence tomography, lymph pred Lymphocytic predominance, CSF OP CSF opening pressure

Table 2 Viral meningitis

ID (Ref)	Author (Year)	Study type, Country	Sex (Age)	PMH/ Comorbidity	Vaccination for VZV	Symptoms/ physical examination	Dermal manifestation	Vaccine (dosage)	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
3, [46]	Burana-sakda (2022)	Case series, Thailand	M (34)	Contracted varicella twice at a young age/ Asthma	No	Neck stiffness, severe headache, Vomiting/T = 36.5c / no focal neurological deficit/ clinically diagnosed with VZV	A vesicular lesion on the left side of his waist (T11)	Inactivated COVID-19 vaccine, First	CSF OP = 17 cmH2O CSF WBC = 185 Cell/mm3 (77% lymphocyte, 19% monocyte, and 2% neutrophil) CSF Glucose = 50 mg/dl CSF prot = 92 mg/dl CSF culture = -	5 days	-	Oral and IV acyclovir	Full recovery after two weeks post-discharge	Negative
4			M (32)	No / Asthma and seroconverted hepatitis B	-	Bilateral temporal headache / Fever (T = 36.5c)	No	Viral vector, First	CSF OP = 18 cmH2O CSF WBC = 288 Cell/mm3 (93% lymphocytes, and 6% monocytes, no neutrophils) CSF glucose = 55 mg/dl CSF prot = 102 mg/dl CSF culture = - CSF VZV PCR = +	5 days	Normal CT scan results	IV Acyclovir	Full recovery after two weeks post-discharge	Negative
5, [47]	You (2022)	Case report, Korea	M (74)	HTN, DM, Left hemiplegia due to past CVA (17 years ago), history of chicken pox in childhood	No	Severe headache and forehead pain, left eyelid swelling and left eye photophobia, itching and tingling sensation on the left side of the face / conjunctival chemosis, hyperemia, and pseudo dritite in the peripheral cornea in the left eye	A vesicular rash on the forehead which progressed rapidly and involved the left side of the scalp, left upper eyelid, and nose	mRNA, second	Serum CRP = 18.97 mg/L Serum WBC = 4.710 cells/uL Serum VZV IgM = +/- CSF WBC = 47 cells/uL with (lymph pred) CSF Prot = 74.5 mg/dL CSF glucose = 86 mg/dl CSF WBC = 50 cells/mm3 (lymph pred) Herpes Zoster PCR = +	5 days	Normal MRI results	IV Acyclovir, topical acyclovir ointment, and Levo-floxacin 1.5% eye drop and mild corneal superficial stromal haze	Six months later his visual activity was 20/63 with stable slit lamp examination and mild corneal superficial stromal haze	Negative
10, [48]	Lizzaro (2022)	Case series, USA	M (54)	-	-	Severe headache, fever, and chills, collapsed at home /	-	mRNA, first	CSF WBC = 50 cells/mm3 (lymph pred) Herpes Zoster PCR = +	1 day	Normal chest CT	Oral acyclovir, high dose IV antiviral	Full recovery at six weeks after diagnosis	Negative

Table 2 (continued)

ID (Ref)	Author (Year)	Study type, Country	Sex (Age)	PMH/ Comorbidity	Vaccination for VZV	Symptoms/ physical examination	Dermal manifestation	Vaccine (dosage)	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
14, [49]	Kerr (2022)	Case report, Germany	M (39)	History of chickenpox as a child	-	Vesicular torso rash, burning occipital headache, fever, nausea, and vomiting	A vesicular rash on the right side of the torso (T10 dermatome), that was beginning to scab over	mRNA, first	Blood mild lymphopenia, Serum CRP = 11 mg/L, CSF WBC = 196 cells/mm3 (lymph pleo) CSF prot = 102 mg/dL	2 Weeks after	Normal CT brain imaging	IV acyclovir	Full resolution of symptoms within 48 of treatment commencement	Negative
15, [50]	Daouk (2022)	Case report, USA	M (12)	No	-	A 1-week history of severe flank and thigh pain, twitching movements, headache, and photophobia	Papulovesicular rash (L1 dermatome, gradually progressed to the L2 area, trunk, and scalp)	mRNA (first dose) and live-attenuated varicella vaccine,	CSF CRP = normal CSF WBC = 252 Cells/mm3 CSF prot = 96 mg/dL CSF and Vesicular PCR for VZV = +	11 days	-	IV acyclovir		
27, [51]	Yun (2022)	Case report, Korea	M (18)	A history of hospital admission because of meningitis of unknown etiology at the age of 6 and no history of chickenpox	Yes	Throbbing headache, Fever up to 38.4 C	No	mRNA, second	Normal blood test, H2O CSF RBC = 6 cells/ul CSF glucose = 59 mg/dL CSF VZV PCR = + (Serum IgG for VZV was positive, but IgM was negative)	7 weeks	Normal chest X-ray and brain MRI	IV Acyclovir	A day after admission, his headache, fever, and myalgia had improved	Positive
28, [52]	Maruki (2021)	Case report, Japan	F (71)	Immunoglobulin A (IgA) nephritis (didn't use immunosuppressive agents), a history of childhood chickenpox	No	Headache and fever / Stiff neck, Kernig's sign and joint accentuation	Painful erythematous patches and vesicles on the right side of umbilicus and back	mRNA, first dose	Normal CSF OP and glucose level Serum CRP = 0.04 mg/dL (NL) CSF WBC = 289 cells/ul (lymph predominance) CSF PROT = 295 mg/dL CSF VZV PCR = +	1 Day	-	IV Acyclovir	Complete recovery and discharge on hospital day 14	Negative

Table 2 (continued)

ID (Ref)	Author (Year)	Study type, Country	Sex (Age)	PMH/ Comorbidity	Vaccination for VZV	Symptoms/ physical examination	Dermal manifestation	Vaccine (dosage)	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
32, [53]	Medhat (2022)	Case report, Emirates	F (46)	Dyslipidemia, A surgery history (left-sided cervical tuberculosis (TB) lymphadenitis)	No	Severe headache, light-headedness, photophobia without phobia, nausea, or vomiting Hypotension (BP = 80/64), low-grade fever / terminal neck stiffness	No	mRNA (as the third, booster, dose after two doses of inactivated vaccine)	Normal CSF glucose level CSF VZV PCR = + CSF WBC = 794 * 10 ⁶ cells/L (lymph pred) CSF PROT = 0.81 g/L	3 weeks	Normal brain CT and MRI	IV Acyclovir	Full recovery	Negative
35, [54]	Koh (2022)	Case report, Korea	M (24)	Childhood varicella infection and aseptic meningitis at 12 years of age		Myalgia and fatigue, headache / positive jolt accentuation and neck stiffness	Small vesicles on left upper arm (erythematous patch with grouped vesicles on C5 dermatome),	mRNA, first	CSF OP = 180 cm H2O CSF WBC = 11 cells/uL (98% lymphocytes) CSF prot = 50.6 mg/dL CSF glu- cose = 53 mg/dL CSF VZV PCR = +				After a week, he reported a mild headache, and his general condition and fever had improved as the systemic VZV reactivation and meningitis resolved	
24, [55]	Ahmad (2021)	Case report, Iraq	F (62)	No	-	Headache, fever, rigor, acute confessional state (The patient was not able to stand up and walk), inability to talk/ suspected viral meningitis	No	mRNA, second dose	Serum CRP = 12.9 CSF WBC = 170 cells/mm3 (lymph pred) CSF prot = 802 mg/dL Viral PCR for Herpes simplex virus both type 1 and 2 were negative	5 days	Brain CT and MRI = NL	Acyclovir vial IV 750 mg three times daily for 14 days	The patient responded very well to the acyclovir, she became conscious again and oriented within two days and 14 days later	-

Table 2 (continued)

ID (Ref)	Author (Year)	Study type, Country	Sex (Age)	PMH/ Comorbidity	Vaccination for VZV	Symptoms/ physical examination	Dermal manifestation	Vaccine (dosage)	Lab findings	Day of onset	Paraclinical	Therapy	Follow up	COVID-19 test
25, [56]	Wiley, 2022	Case report, USA	F (17)	Migraine	-	severe headaches, fever, visual loss in both eyes	No	mRNA, first dose	Blood ESF = 30 mm/h CSF WBC = 48 cells/ μ L CSF prot = 23 mg/dL A CSF cytomegalovirus (CMV) PCR was positive, but the patient had no clinical evidence for ocular or systemic CMV/ Serum herpes simplex virus (HSV) 1/2 IgM = +	2 days	MRI with contrast of the brain and orbits showed minimal papilledema but was otherwise normal/ Fluorescein angiogram showed severe leakage from the disc in the right eye with, mild leakage from the disc in the left eye, and wreath-like choroidal hyperfluorescence of the posterior pole in both eyes	Valacyclovir 1000 mg twice per day for 10 days and Acetazolamide 750 mg twice per day for 30 days	A follow-up exam in the clinic about one month after discharge showed visual acuity of 20/20, and resolution of the optic disc edema and peripapillary flame hemorrhage. OCT showed resolution of the optic nerve edema OU	Negative

Prot Protein, CT scan Computed tomography, MRI Magnetic resonance imaging, CSF Cerebrospinal fluid, CRP C-reactive protein, OCT Optical coherence tomography, lymph pred lymphocytic predominance, CSF OP CSF opening pressure

Table 3 (continued)

Author (Year)	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Were diagnostic tests or assessment methods and the results clearly described?	Was the current clinical condition of the patient on presentation clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	SUM
Ganapathiram et al. (2022) [30]	yes	no	yes	yes	yes	yes	yes	yes	7
Torrebalba-Acosta et al. (2021) [31]	yes	yes	yes	yes	yes	yes	no	yes	7
Gogu et al. (2022) [32]	yes	yes	yes	yes	yes	yes	yes	no	7
Sumi et al. (2022) [33]	yes	yes	yes	no	yes	no	no	no	4
Tagini et al. (2022) [34]	yes	yes	yes	yes	yes	yes	yes	no	7
Saito et al. (2021) [35]	yes	yes	yes	yes	yes	yes	no	yes	7
Koh (2022) [54]	yes	yes	no	yes	yes	yes	no	yes	6
Kato (2023) [42]	yes	yes	yes	yes	yes	yes	no	yes	7
Kularathna (2024) [43]	yes	yes	yes	yes	yes	no	no	no	5
Ramesh, (2023) [44]	yes	yes	yes	yes	yes	no	no	yes	6

Table 4 Quality assessment of case series

Author (Year)	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	SUM
Chan 2022 [38]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	8
Chen 2023 [40]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	-	8
Buranasakda 2022 [46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	9
Fernandes 2022 [25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	9
Ghang 2022 [26]	No	No	No	Yes	No	No	No	No	No	-	1
Lazzaro 2022 [48]	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	-	7

vaccine-induced meningitis. The statistic for this condition was 62.5% for drug-induced and 37.5% for viral meningitis. These statistics were lower for other vaccines such as Moderna, Covax, and AstraZeneca. Also, our investigation showed very thinkable information: only three of 32 patients had a positive COVID test after vaccinations. This finding claimed that meningitis after vaccinations may be related to the vaccines, not the disease. Furthermore, among all selected cases, most patients hadn't a remarkable past medical history, except four had dyslipidemia, and two had migraines. Regarding time interval after receiving vaccines, our included cases showed most of the symptoms of meningitis appeared after the first dose of vaccines, which were 55.0% (11 of 20 patients) for drug-induced, and 58.8% (five out of 10 patients) for viral meningitis.

Vaccine-induced meningitis

Drug-induced meningitis, as a subtype of aseptic meningitis, is defined as an inflammatory disorder affecting the meninges, and it can sometimes have an iatrogenic origin, meaning it is caused by medical intervention or treatment [60]. Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, or intravenous immunoglobulin (IVIg) are examples of medications that have been associated with this [61]. Our review evaluated 20 patients diagnosed with aseptic meningitis; most received the Pfizer COVID-19 vaccine. The presented symptoms among these patients were headaches in 18 of 20 patients. This symptom is prevalent in these patients based on the typical case of aseptic meningitis [18]. However, headaches could be an adverse effect of vaccines. Garg and Paliwal [62] reported a spectrum of COVID-19 complications such as headache, myositis, Guillain-Barre syndrome, and Cranial nerve palsies. In the context of COVID-19 vaccine-related neurological side effects, researchers have proposed "molecular mimicry" as a potential pathogenic mechanism [12]. This mechanism suggests that the spike proteins generated by the vaccines, against which antibodies are produced, can share similarities with specific molecules present on the surfaces of cells, such as sialic acid-containing glycoproteins and gangliosides. As a result, the spike proteins may have the ability to bind to these cell surface molecules, leading to potential adverse events. This molecular mimicry further supports the biological plausibility of the neurological side effects associated with the COVID-19 vaccine [63]. Based on the discussed context, these sharing surface molecules may play a role in aseptic meningitis, and the cause of this event after receiving the first dose of vaccines is still unclear. However, it can be assumed that the first vaccine exposure often led to some adverse effects. In the molecular view of aseptic meningitis, the

central laboratory findings among aseptic patients were increased C reactive protein (CRP), CSF protein levels, and pleocytosis in 9 (45.0%), 11 (55.0%), and 13 (65.0%) patients. Many of our reported cases of drug-induced were healed with methyl prednisone, Dexamethasone, and NSAIDs as significant therapeutic regimens. These regimens are commonly used because the immune system responds to some molecules, and these drugs could attenuate the immune system.

Viral meningitis

Our investigation identified 12 cases of viral meningitis, with 10 cases attributed to VZV. One other was tested positive for CSF CMV PCR and serum HSV 1/2 IgM. In the last patients, the potential underlying viral agent was not identified. Still, considering a lymphocytic WBC predominance in CSF analysis and response to antiviral therapy, the authors suspected a viral etiology for meningitis. Most patients presented with similar initial symptoms, including headache, nausea, vomiting, and vesicular rashes at the T10 dermatome, commonly observed in the early stages of meningitis. Other manifestations among the viral cases included neck stiffness, photophobia, and fever. These clinical features are typical indicators of meningitis and warrant prompt attention and appropriate management to ensure optimal patient outcomes. Our investigations on the CSF culture of patients with viral meningitis revealed varicella-zoster virus, and four of ten septic patients noted a history of chickenpox. Buranasadka et al. found two VZV meningitis cases after receiving COVID-19 vaccines [64]. One of the two VZV cases in their study had contracted VZV in childhood, and the authors hypothesized this condition as reactivation of VZV after vaccination. The underlying mechanism of this reactivation may resemble the study conducted by Psychogiou et al. [65], in which it has been suggested that the agency responsible for varicella zoster reactivation following COVID-19 vaccination might bear similarities to immune reconstitution inflammatory syndrome (IRIS) observed in HIV patients after receiving antiretroviral therapy. In HIV patients, antiretroviral drugs can worsen latent or occult infections as the immune system strengthens and responds to previously dormant pathogens. Similarly, it is postulated that COVID-19 vaccination might trigger a similar response, potentially reactivating latent varicella-zoster virus in specific individuals. This hypothetical resemblance to IRIS in the context of antiretroviral therapy highlights the importance of further research to understand the complexities of vaccine-related immune responses and their potential implications on latent infections. Similar to the underlying cause of the reactivation of VZV, You et al. [66] suggest an identical mechanism. Their study

suggested that vaccination using COVID-19 mRNA vaccines may trigger an immunomodulatory response that could potentially reactivate dormant Varicella Zoster Virus (VZV). Vaccination stimulates the immune system, leading to a robust T-cell response. Specifically, vaccination with BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) results in an increased cellular response, leading to the production of spike-specific CD8+ T cells and T helper type 1 CD4+ T cells, particularly after receiving a booster dose [66]. One plausible hypothesis suggests that, due to the massive shift of naive CD8+ cells triggered by SARS-CoV-2 mRNA vaccination, VZV-specific CD8+ cells might become temporarily unable to regulate the dormant VZV effectively. This temporary imbalance in the immune system may create an environment conducive to VZV reactivation.

Study limitations

Our study has some limitations that readers and the scientific community should note. First, our sample size was small, which may introduce bias and limit the generalizability of our findings. Second, patients' drug history was insufficiently detailed, and relevant studies were not accurately referenced, potentially affecting the interpretation of lumbar puncture results and vaccine efficacy. Third, the positive outcome of lumbar puncture for VZV does not indicate the exact timing of infection; it could have occurred before or after vaccination. The available data did not provide enough support to draw a definitive conclusion.

Conclusion

Overall, our study suggested that meningitis is a critical but not devastating complication of COVID-19 vaccination. Almost all patients responded well to common agents for managing vaccine-induced meningitis. It is recommended to monitor patients with a history of chickenpox after COVID-19 vaccination for the development of meningitis.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12879-024-10043-6>.

Supplementary Material 1.

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Authors' contributions

AHA, and AS designed the project. AHGH, KE, HHA, CA, and MAE conducted systematic search and screening. AHA, AGH, and AB performed data extraction. AHA, AGH, AS, AB wrote the manuscript. All the authors read and confirmed the final version of the paper.

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Declarations

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