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THROMBOCYTOPENIC THROMBOTIC PURPURA FOLLOWING CHADOX1 NCOV-19 VACCINATION IN NORTHEAST INDIA: A CASE SERIES

Medicine

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ABSTRACT

Widespread vaccination to mitigate severe illness due to the COVID-19 pandemic has occurred despite rare adverse events such as Thrombotic Thrombocytopenic Purpura (TTP) following vaccination(1). TTP is a potentially fatal disorder defined by profound deficiency of ADAMTS13 with resulting platelet aggregation and microvascular thrombosis(2). This study reviews five cases of TTP following ChAdOx1 nCoV-19 (Covishield) vaccination from Manipur, India, with emphasis on clinical presentations, management, and outcomes. This is a retrospective case series with five female patients, aged 25–48 years with TTP developing 2–8 weeks post-vaccination. Diagnosis was established using clinical features, laboratory results, and PLASMIC scores, excluding congenital or drug-induced TTP. Treatment included high-dose steroids, plasmaphoresis and Rituximab. Reslults showed One patient died following 33 days of ICU treatment despite aggressive treatment, and four others recovered after 9-13 cycles of plasma exchange; none relapsed during follow-up. The study highlights the critical role of early diagnosis and intervention, such as plasmapheresis and immunosuppressive therapy, in decreasing mortality. More studies are required to clarify the mechanistic underpinnings of vaccine-related TTP so as to optimize the management of vulnerable patients.

KEYWORDS

COVID-19 vaccination, thrombotic thrombocytopenic purpura, ChAdOx1 nCoV-19, ADAMTS13 deficiency, plasma exchange.

INTRODUCTION

The COVID-19 pandemic, which is caused by the SARS-CoV-2 virus, led to a worldwide urgent vaccination campaign, which led to the rapid provisioning of vaccines across the globe. Although the benefits of vaccination to prevent severe COVID-19 are unquestionable, there have been rare adverse events. It has been associated with new onset of thrombotic microangiopathy (TMA), and there have been recent reports of markedly increased rates of thrombotic thrombocytopenic purpura (TTP), a cause of potentially fatal TMA developing after vaccination[3]. TTP, especially aTTP, is characterized by a severely reduced level of activity of the von Willebrand factor regulator ADAMTS13, resulting in platelet clumping and microvascular thrombus formation. While rare, the condition can present with life-threatening sequelae, including microangiopathic hemolytic anemia, thrombocytopenia, and multi-organ dysfunction[4].

In particular, adenovirus vector-based (ChAdOx1 nCoV-19) and mRNA (BNT162b2) COVID-19 vaccines have been associated with both de novo and relapsing cases of TTP[5]. Most adverse events related to vaccines are mild, however, the development of immune-mediated TTP is a great concern because of its risk for quick progression and high mortality in the absence of timely treatment[6]. This communication reviews 5 cases of Thrombotic Thrombocytopenic Purpura (TTP) following ChAdOx1 nCoV-19 vaccination in Manipur, Northeastern India and describes the potential mechanisms and current understanding of this rare complication.

Patients and Methods

In this retrospective case series we assess the clinical features, treatment response, and complications of 5 patients who developed TTP after COVID-19 vaccination. The study was carried out in a tertiary care hospital in Imphal, Manipur, on patients diagnosed and treated from October 2021 to October 2022 and followed up till December 2024. This study's main objective is to report clinical features, rates of recovery, complications, and mortality in patients with vaccine-associated TTP, with secondary outcomes of length of hospitalization and readmission rates.

Only patients with a history of confirmed TTP diagnosis following vaccination were included in the study, which relied on at least a positive Plasmic score, clinical signs, peripheral blood laboratory results and detection of schistocytes on blood smear. The study only considered participants who were adults (18 years or older) who had received a COVID-19 vaccine and developed TTP in a specifically window of time after vaccination. Patients with a known history of congenital TTP, drug-induced TTP, or other reported non-vaccine TTP aetiologies were excluded from the analysis, as were those with incomplete clinical or follow-up data. We retrospectively extracted the data from the medical records of the patients, including demographic data, vaccination (vaccine type and date), clinical symptoms, laboratory findings, treatment protocol, and outcome. Particular emphasis was placed on various parameters including patient age, gender, comorbidities, initial presentation, the Plasmic score at diagnosis and therapeutic interventions (e.g., plasma exchange, immunosuppressive therapy). They were trained with a sample containing data points on hospitalization length, complications and readmissions.

The main outcome measures were recovery rate, complications and mortality. The recovery rate was defined as either complete resolution or significant improvement in clinical symptom and laboratory markers at the end of treatment. Complications were defined as organ injury, relapses of TTP, or any other vaccine-related adverse events. Mortality was defined as death that occurred during the study period as a result of complications due to TTP. Secondary outcome measures were length of same hospitalization and readmission rate (defined as number of patients recrossing to the hospital because of complications or relapses of TTP symptoms). Data were summarized using descriptive statistics. Patient confidentiality was maintained, and informed consent was obtained from all patients or their legal guardians to use their medical data for research purposes.

This study has several limitations, which includes small sample size and being a single-center study,limiting the generalization of the findings. Also being a retrospective analysis, the study is only

dependent on the accuracy of the data available.It cannot establish direct causality due to the nature of the design.

RESULTS

This case series involving five female patients aged 25 to 48 years (mean age 36.8 years) with significant complications after receiving Covishield, a COVID-19 vaccine. The time from vaccination to hospital admission ranged from 2 to 8 weeks, with average being of 4.6 weeks. Out of five, four had received their second dose, and one had received the first dose. All patients presented with severe symptoms which includes fever, headaches, proptosis, seizures, and altered sensorium. Vegetative states and dermatological manifestations, such as petechiae and purpuric patches, were also seen in several cases.

On clinical examination, Glasgow Coma Scale (GCS) scores ranged from 3/15 to 12/15. Common findings included pallor, petechiae, purpura, and in one case, massive purpuric patches. Past medical histories were largely insignificant except for hypertension in two patients and asthma in one. All patients tested negative for COVID-19. Investigations revealed significant thrombocytopenia (platelet counts ranging from 3,200 to 10,400), elevated lactate dehydrogenase levels (2,196–4,012), and schistocytes on blood smears (6–8%), indicating microangiopathic hemolysis. Imaging studies uncovered severe neurological complications, such as hemorrhages, infarcts, or thrombosis. PLASMIC score was used to assess thrombotic microangiopathy. The score of 6 to 7, indicated high risk.The ADAMTS-13 test couldn't be performed due to the nonavailability and financial restraint.

Management involved high-dose steroids (1 gram for 3 days followed by tapering over 3–4 weeks), plasma exchange (9–13 cycles), and Rituximab (four doses). Despite this aggressive treatment, the outcomes varied. Four patients responded favorably, in which clinical improvement was noted by the 7th to 9th cycles of plasma exchange and complete recovery by the 9th to 13th cycles. One patient, although hematologically improved, failed to recover clinically and succumbed after prolonged ICU care.

Follow-up data indicated that survivors remained stable, with no relapses being reported. Unfortunately, the patient who did not recover clinically passed away after a two-month ICU stay.

Category	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/Sex	25/F	48/F	26/F	45/F	40/F
Time from Vaccination	4 weeks (2nd dose)	8 weeks (2nd dose)	2 weeks (1st dose)	6 weeks (2nd dose)	3 weeks (2nd dose)
Presenting Symptoms	Fever, headache, proptosis, altered sensorium	Purpuric patches, altered sensorium, ITP	Fever, cola-colored urine, seizures, vegetative state	Seizures, vegetative state	Purpuric patches, vegetative state
Examination Findings	GCS: 8/15, pallor, petechiae, mild icterus	GCS: 12/15, pallor, petechiae, purpura	GCS: 3/15, pallor, icterus, petechiae, non-coherent	GCS: 7/15, petechiae, purpura, non-coherent	GCS: 3/15, massive purpuric patches, non-coherent
Hb: Hematocrit: Schistocyte: Platelets: LDH: S.Creatinine: Imaging: Others:	10 31 3.2% 6000 2196 1.2 hemorrhage at the left cavernous sinus -	9.6 30.4 6% 5000 2258 1.6 thrombosis at the left transverse sinus -	8.2 27 5.4% 3200 3554 1.4 infarction in the left hemisphere APLA+	6 25 4% 7400 4012 1.0 infarction in the left hemisphere	7 28 6.2% 10400 3047 1.2 infarct in the right hemisphere
PLASMIC Score	6	6	7	7	7
Past History	None	Hypertension	Asthma	Hypertension	None
Management	Steroids, plasma exchange (12 cycles), Rituximab	Steroids, plasma exchange (9 cycles), Rituximab	Steroids, plasma exchange (13 cycles), Rituximab	Steroids, plasma exchange (12 cycles), Rituximab	Steroids, plasma exchange (12 cycles), Rituximab
Recovery	Recovery after 12 cycles	Recovery after 9 cycles	Recovery after 13 cycles	Recovery after 12 cycles	Blood picture improved, clinical recovery failed
Follow-Up/Relapse	Regular follow-up, no relapse	Regular follow-up, no relapse	Regular follow-up, no relapse (continued HCQ)	Regular follow-up, no relapse	ICU care for 2 months, discharged, expired

DISCUSSION

An association between TTP and vaccination was published after influenza, pneumococcal, H1N1, and rabies vaccines. The great majority of these cases took place within two weeks of vaccination, particularly in vaccines which target the viral agents. This pattern suggests a triggering of vaccine-induced immune activation and possibly autoantibody formation or molecular mimicry in the pathogenesis of TTP[7].As highlighted by Doyle et al., Autoimmune conditions such as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), Miller-Fisher syndrome, Guillain-Barré syndrome, and immune thrombocytopenia (ITP) have been reported post-COVID-19 vaccination, the overlap of TTP with VITT (characterized by thrombocytopenia, thrombosis, and neurological symptoms) makes it difficult to diagnose[8]. Delayed recognition of TTP could result in a failure to initiate plasmapheresis promptly—a first-line therapy in TTP but a second-line treatment in VITT—significantly increasing morbidity and mortality risks[9].

Two primary hypotheses have been proposed to explain the pathophysiology of de novo TTP following vaccination. One speculation, put forward by Deucher et al., is that vaccination serves as a trigger for an as yet undiagnosed subclinical TTP state, provoking a florid episode. This finding is consistent with the delayed onset of immune responses that are generally seen, with symptoms often appearing days to weeks after vaccination[10]. The second hypothesis, considered by Eric M Ostertag. and others, a process involving molecular mimicry occurs, wherein vaccine components or adjuvants stimulate production of autoanti-bodies targeting ADAMTS13, which in turn causes decrease in enzymatic activity and and subsequent microvascular thrombosis[11]. Furthermore, Schiepatti et al. highlighted that for patients with relapsing or congenital TTP, vaccination may act as a "second hit" by inducing inflammation or an immune response, triggering an acute episode[12].

Interestingly, most cases of vaccine-associated TTP reviewed by Deucher et al. showed no significant predisposing factors beyond vaccination[10]. However, a few exceptions were noted, such as a case with a maternal history of immune thrombocytopenia, another with connective tissue disease[13-14], and one involving a patient with prior malignancy[15]. These cases suggest that an underlying predisposition to autoimmunity may amplify the immune response post-vaccination, precipitating TTP. Importantly, one patient who had an ischemic stroke after the first vaccine dose subsequently developed de novo TTP after the second dose, pointing to a possible early hypercoagulable state unrecognized after the initial vaccination[16].

The clinical outcomes in these cases varied significantly based on the timeliness and modality of treatment. While most patients achieved remission with plasmapheresis, steroids, and rituximab. Furthermore, early initiation of plasmapheresis, especially in cases of TTP, is paramount, with mortality rates of up to 80–90% when untreated[6]. Alternative therapies have excelled in some studies like caplacizumab, other immunosuppressives due to situations in which the morbidity regarding plasmapheresis is a major concern[17].

The long-term implications of vaccination in TTP patients remain complex. Many cases were advised against completing their vaccination series due to relapse concerns or potential immune suppression post-treatment with rituximab. However, Deucher et al. documented a case where a patient successfully received the second

dose of the BNT162b2 vaccine without adverse effects, emphasizing the role of careful monitoring, including an ADAMTS13 activity threshold, in determining vaccine safety for such patients[10]. Doyle et al. further noted no increase in TTP incidence during peak COVID-19 vaccination periods in England, suggesting that these events may occur at rates consistent with the general population's expected baseline[18].

Additionally, Schiepatti et al., in their small cohort study, observed no significant changes in ADAMTS13 activity or inhibitor levels at days 21 and 60 post-COVID-19 vaccination among patients with a known history of immune TTP[12]. This finding supports the notion that vaccination can be safely administered under controlled circumstances in this high-risk population.

CONCLUSION

ChAdOx1 nCoV-19 (Covishield) vaccination associated Thrombotic Thrombocytopenic Purpura (TTP) is uncommon but poses major clinical hurdles in diagnosis and management. We believe that this case series emphasizes the importance of early recognition of TTP in those patients who present with neurological and hematological manifest outside and in temporal relation to vaccination. All patients were treated with high-dose steroids and plasma exchange, alone or combined with Rituximab; all but one died after a prolonged intensive care unit stay and were deemed normal at follow-up. Early initiation of plasmapheresis and immunosuppressive therapy will improve outcomes and decreases mortality. More research is needed to understand the mechanisms involved in vaccine-associated TTP, including possible immune activation or molecular mimicry, and to help inform optimized management strategies in at-risk patients. While the risk for such rare adverse effects exists, the benefits of COVID-19 infection (severe illness and death prevention) outweighs potential harm — and it is critical to monitor closely to prevent any adverse effects in the population at-risk individuals

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