Fatal Case of Acute Pulmonary Embolism due to Venous Thrombosis after COVID-19 Vaccination: Based on Forensic Postmortem Examination

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We present an unexpected fatal case of pulmonary embolism due to venous thrombosis after vaccination for coronavirus disease 2019 (ChAdOx1 nCov-19). The deceased was a 64-year-old woman with Alzheimer disease. The deceased had fever shortly after vaccination, and presented sudden dyspnea and died 8 days after vaccination. On postmortem examination, pulmonary embolism and venous thrombosis were noted in deep veins of both lower legs. Even though the psychomotor function of the deceased became fragile due to Alzheimer disease, the deceased was not bed-ridden, and major known risk factors related to venous thrombosis were not explicit in this case. Because there are not enough data related to vaccination and thrombosis, we hope that this case would be helpful in unraveling pathogenesis of venous thrombosis after vaccination and in determining whether there is any association between thrombosis and vaccination.

Key Words: COVID-19 vaccines; Pulmonary embolism; Venous thrombosis

Introduction

The coronavirus disease 2019 (COVID-19) has become a global pandemic since 2020; more than 146 million people have been confirmed as COVID-19, and more than 3 million people have died due to this disease [1]. Currently, the all cause mortality of COVID-19 is relatively low in South Korea because of the low prevalence of the disease, but as the pandemic continues to evolve with additional waves, the mortality and morbidity related to this disease will be higher [2]. Furthermore, severe COVID-19 is common in the elderly

or in those with comorbidities including hypertension, cardiovascular disease, chronic respiratory disease and diabetes [3]. Hence, it is expected that vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) would play a critical role in controlling the COVID-19 pandemic.

The COVID-19 vaccine (ChAdOx1 nCov-19) was introduced at the end of February 2021 in South Korea. It was shown in the clinical trials that the vaccine has an acceptable safety profile, and homologous boosting increased antibody responses [4]. However, we recently encountered an unexpected fatal case

after vaccination; the cause of death was determined as pulmonary embolism due to venous thrombosis, based on postmortem examination. Similar events involving venous thrombosis after vaccination have also been reported in other countries [5,6]. This case is significant because there are insufficient data related to the adverse events after vaccination. Therefore, our findings will be helpful in unraveling the pathogenesis of thrombosis after vaccination and its association.

Case Report

The deceased was a 64-year-old woman who was staying at a care hospital because of her dementia due to Alzheimer disease. Six years ago, the deceased was diagnosed with dementia due to Alzheimer disease, and recently, it had become worse in terms of psychomotor function. Therefore, the deceased was admitted to a care hospital. The deceased needed assistance and care for carrying out her daily routine activities such as eating and walking, but she was not bed-ridden. The deceased received COVID-19 vaccination (ChAdOx1 nCov-19), and consequently experienced fever that night and the next morning. Then the deceased seemed to have a poor appetite at meals but was otherwise unremarkable. Eight days after vaccination, the deceased was suddenly complained of severe dyspnea with a pale complexion, while sitting on the sofa in the afternoon. The deceased was transported immediately

to a hospital, but the clinical course became worse and unstable, and then the deceased ultimately expired.

On external examination, the deceased was well nourished and clean. The body mass index was 23.6 kg/m² (height, 166 cm; weight, 65 kg). The vaccination injection site was observed on the right deltoid area. No injury was identified and otherwise, it was unremarkable.

On internal examination, cerebral atrophy was observed (1,130 g). Microscopically, loss of neurons with vacuolar degeneration, neurofibrillary tangles, amyloid plaques, and cerebral amyloid angiopathy were observed, which is consistent with Alzheimer disease. Saddle thromboemboli were observed in the main trunk of the pulmonary arteries and the peripheral pulmonary arteries of both lungs (Fig. 1A). Cardiomegaly (500 g) was observed; the wall thickness of the left ventricle, interventricular septum and right ventricle was 1.3 cm, 1.3 cm, and 0.3 cm, respectively. The valvular circumference of the tricuspid, pulmonary, mitral and aortic valves was 12.7 cm, 7.5 cm, 11.0 cm, and 7.2 cm, respectively. The left and right coronary arteries were unremarkable. The posterior tibial vein and deep perforating veins of the right and left lower legs revealed diffuse venous thrombosis (Fig. 1B). Other main veins including inferior vena cava and major branches were unremarkable. No thrombus was observed in dural sinuses and major cerebral veins. Microscopically, acute thrombi were observed in the

Fig. 1. Pulmonary embolism is observed in the main trunk of the pulmonary arteries of both lungs (A), and venous thrombosis is observed in the posterior tibial vein of both lower legs (B).

pulmonary artery (Fig. 2A), and veins of both lower legs (Fig. 2B), and the apex of the right ventricle of the heart (Fig. 2C). The thyroid revealed two nodules in the background of Hashimoto's thyroiditis; an ovoid shaped nodular hyperplasia (4.5×3.0×2.5 cm) in left lobe, and an encapsulated nodule with calcification (3.0×2.0×2.0 cm) in right lobe, which microscopically, was focally invasive encapsulated follicular variant of papillary carcinoma. The injection site of vaccination revealed focal hemorrhages in the fibroadipose tissue (Fig. 2D) and was otherwise unremarkable. The spinal cord and nerve roots, and sural nerves were also unremarkable.

On the postmortem ancillary testing, levetiracetam, dihydrocodeine, chlorpheniramine, and ephedrine were detected, and their concentrations in the blood were

within the therapeutic levels. Postmortem biochemistry of the vitreous humor revealed increased level of glucose (204 mg/dL), and HbA1c (6.4%), suggesting the possibility of prediabetes or diabetes mellitus, but the blood level of ketone bodies was unremarkable. Postmortem thyroid function test revealed slightly increased level of T3 (triiodothyronine) and thyroid stimulating hormone. C-reactive protein (CRP) was 3.41 mg/dL. Postmortem tryptase test revealed unremarkable result (6.2 µg/L). Anti-platelet antibody, platelet associated antibody, and anti-heparin/platelet factor 4 (PF4) antibody tests were performed belatedly 36 days after death using postmortem blood sample, which was kept as whole blood, not as serum and was not preserved anticoagulated, and the results were

Fig. 2. On microscopic examination, acute thromboemboli along with increased number of white blood cells are identified in the pulmonary artery (H&E, ×100) (A), and in the right ventricle of the heart (H&E, ×100) (B). Acute thrombi are also observed in the posterior tibial vein of the right lower leg (H&E, ×100) (C). Focal hemorrhage is identified on the subcutaneous adipose tissue at the site of vaccination (H&E, ×100) (D).

negative.

The cause of death was determined as pulmonary embolism due to venous thrombosis. Anaphylaxis related to COVID-19 vaccination was unlikely based on the deceased's clinical course, the postmortem findings and ancillary testing.

Discussion

This case illustrates an unexpected fatal case of pulmonary thromboembolism due to venous thrombosis occurred on the eighth day after COVID-19 vaccination (ChAdOx1 nCov-19). Acute thromboemboli were identified in the main trunk and branches of both pulmonary arteries and the veins of both lower legs. No thrombus was observed in the dural sinuses or cerebral veins. The deceased was a 64-year-old woman who was hospitalized for more than one year because of aggravated dementia. There was no past medical history other than dementia due to Alzheimer disease. The deceased met the requirements to undergo vaccinated because the deceased had not been ill at that time point. Although the deceased needed assistance for routine daily activities, she was not bed-ridden. After vaccination, the deceased had fever for a short duration and then she had no specific symptoms, but the deceased might not have been in good condition because she seemed to have lost her appetite.

Various acquired risk factors for development of venous thrombosis and pulmonary thromboembolism are well known; >48 hours limited mobility in last month, recent prior hospitalization, recent surgery, recent malignancy, recent infection, admission with non-venous thromboembolism-related diagnosis (immediately prior event), recent central venous catheter, prior venous thromboembolism, recent intensive care unit discharge, recent intubation, recent hormonal therapy, recent fracture, recent chemotherapy, recent heart failure, and recent cardiac procedures [7]. In this case, a focally invasive encapsulated follicular variant of papillary carcinoma, was incidentally identified in the thyroid on postmortem examination, but it is considered an indolent tumor with excellent prognosis [8]. Therefore, it is unlikely to be considered as a risk factor of recent carcinoma. Besides, the deceased

had no past medical history and no definite acquired risk factors.

A study on pulmonary embolism and venous thrombosis in South Korea revealed strong association between season and pulmonary embolism incidence [9]. There are several plausible explanations for this; contribution to increase in blood viscosity by inhalation of cold air, increased incidence of respiratory infection, aggravation of pulmonary diseases and sepsis in winter, and aggravation of air pollution during winter. However, recent reports revealed that health prevention measures against COVID-19 led to decreased incidences of respiratory viral diseases [10–12]. This case did not occur in the middle of winter. The care hospital was also under health protection measures against the COVID-19 pandemic. The deceased's clinical course before and after vaccination revealed that she had no recent infection or illness, except for fever shortly after vaccination. Hence, it is unlikely that seasonal variation including infection, might have contributed to the venous thrombosis.

It has been suggested that coagulation is associated with inflammatory responses during infection, that venous stasis is a part of inflammatory response for migration of leukocytes, and that inflammation leads to coagulation through complex mechanisms [13,14]. Systemic inflammation, followed by increased level of CRP and other cytokines, is associated with an increased risk of venous thromboembolism [13,14]. In this case, no recent infectious diseases were identified in the postmortem findings and the clinical course, but elevation of CRP was observed as 3.41 mg/dL. This finding might be a response to systemic inflammation provoked by COVID-19 vaccination, which is supported by the finding that the deceased had fever and then appeared not to be in good condition after vaccination. In addition, given that the COVID-19 vaccine (ChAdOx1 nCov-19) was developed using the recombinant adenoviral vector [4], adenovirus-induced thrombocytopenia can occur due to adenovirus binding to activate platelets and endothelial cells [15,16]. Therefore it is possible that the immune response after vaccination might have been a trigger for venous thromboembolism in this case.

Hashimoto's thyroiditis observed in this case, might

raise the following question; is the elevated CRP level (3.41 mg/dL) related to inflammatory thyroid disease? A previous study investigated the prevalence of serum CRP levels in inflammatory and noninflammatory thyroid disease [17]. A few patients with Hashimoto's thyroiditis had elevated CRP levels, but there was no significant difference between them and the control group [17]. Given that the deceased had systemic responses such as fever and was not in good condition after vaccination, elevated CRP would be related to the systemic response after vaccination rather than the deceased's thyroid disease.

Recently the occurrence of thrombosis and thrombocytopenia after COVID-19 vaccination (ChAdOx1 nCoV-19) has been reported [4,18–20]. It occurred 5–16 days after vaccination along with thrombosis such as cerebral venous thrombosis, splanchnic-vein thrombosis, pulmonary embolism, other thrombosis and disseminated intravascular coagulation. The authors suggested that the vaccination might have induced a kind of immune thrombotic thrombocytopenia that is mediated by platelet-activating antibodies against platelet factor [4,20]. Anti-heparin/PF4 antibody test were also done in this case, but the result was negative. However, given that anti-heparin/PF4 antibodies remain stable at 4°C for four days in serum, EDTA and citrate samples [21], there are limitations in the interpretation of the results because the antibody tests were performed belatedly 36 days after death. Moreover, because the postmortem sample was stored as whole blood, not as serum, and was not preserved anticoagulated, it is unclear whether it would remain stable without degradation caused by postmortem changes.

Recently, it is suggested that vaccine-induced immune thrombotic thrombocytopenia (VITT) would not be caused by antibodies against the SARS-CoV-2 spike protein (used in all vaccines) but induced by the adenovirus vector and/or other PF4-DNA interactions, and that impurities and EDTA might be an important cofactor for the degree of acute inflammatory response after vaccination [22]. Some healthy healthcare workers reported skin reactions after vaccination, which seemed to be similar to symptoms of serum sickness or capillary leakage; it was first observed on day 1, then

reached its peak on day 4, and was resolved by day 9 [22]. And increased number of white blood cells were observed in a cerebral vein thrombus of a VITT patient, which supports the theory of triggered formation of procoagulant neutrophil extracellular traps [22]. In this case, there was no detailed medical records revealing the deceased's daily medical condition, and because of dementia due to Alzheimer disease, it would be impossible to report any dermal abnormality spontaneously. No explicit dermal abnormalities were identified on postmortem examination. As the study showed, this case also revealed similar findings; thrombi from pulmonary trunk and right ventricle of the heart revealed an increased number of white blood cells (Fig. 2B) and focal hemorrhage was observed at the site of vaccination. However, whether or not the possibility of VITT should be considered in this case seemed to be inconclusive.

In summary, we presented an unexpected case of fatal pulmonary embolism with venous thrombosis after COVID-19 vaccination (ChAdOx1 nCoV-19). Currently there is no definite evidence to support the causation relationship between venous thrombosis and the administration of the vaccine. However, the absence of evidence cannot be the evidence of absence, and recent studies suggested a possible association. In addition, we would like to suggest for postmortem examination in a fatal case of vaccination; to examine the main venous system including dural sinuses and cerebral veins, and splanchnic veins, to keep postmortem blood as serum or EDTA and citrate samples, and to review clinical course and manifestations after vaccination together with postmortem findings.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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References

1. World Health Organization. WHO coronavirus (COVID-19) Dashboard. [cited 2021 Apr 30]. Available from: <https://covid19.who.int/>.
2. Soneji S, Beltran-Sanchez H, Yang J, et al. Population-level death rates from novel coronavirus (COVID-19) in South Korea. *Asia Pac J Public Health* 2021 Feb 9 [Epub]. <https://doi.org/10.1177/1010539521993670>.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323:1239-42.
4. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99-111.
5. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021 Apr 9 [Epub]. <https://doi.org/10.1056/NEJMoa2104840>.
6. Update on the safety of COVID-19 vaccine AstraZeneca [Internet]. Cambridge: AstraZeneca; 2021 [cited 2021 Apr 30]. Available from: <https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-the-safety-of-covid-19-vaccine-astrazeneca.html>.
7. Spencer FA, Emery C, Lessard D, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. *J Gen Intern Med* 2006;21:722-7.
8. Liu J, Singh B, Tallini G, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. *Cancer* 2006;107:1255-64.
9. Hong J, Lee JH, Lee JY, et al. Prominent seasonal variation in pulmonary embolism than deep vein thrombosis incidence: a Korean venous thrombosis epidemiology study. *Korean J Intern Med* 2020;35:682-91.
10. Soo RJ, Chiew CJ, Ma S, et al. Decreased influenza incidence under COVID-19 control measures, Singapore. *Emerg Infect Dis* 2020;26:1933-5.
11. Lai CC, Chen SY, Yen MY, et al. The impact of the coronavirus disease 2019 epidemic on notifiable infectious diseases in Taiwan: a database analysis. *Travel Med Infect Dis* 2021;40:101997.
12. Partridge E, McCleery E, Cheema R, et al. Evaluation of seasonal respiratory virus activity before and after the statewide COVID-19 shelter-in-place order in Northern California. *JAMA Netw Open* 2021;4:e2035281.
13. Schmidt M, Horvath-Puho E, Thomsen RW, et al. Acute infections and venous thromboembolism. *J Intern Med* 2012;271:608-18.
14. Smeeth L, Cook C, Thomas S, et al. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. *Lancet* 2006;367:1075-9.
15. Othman M, Labelle A, Mazzetti I, et al. Adenovirus-induced thrombocytopenia: the role of von Willebrand factor and P-selectin in mediating accelerated platelet clearance. *Blood* 2007;109:2832-9.
16. Stone D, Liu Y, Shayakhmetov D, et al. Adenovirus-platelet interaction in blood causes virus sequestration to the reticuloendothelial system of the liver. *J Virol* 2007;81:4866-71.
17. Pearce EN, Bogazzi F, Martino E, et al. The prevalence of elevated serum C-reactive protein levels in inflammatory and noninflammatory thyroid disease. *Thyroid* 2003;13:643-8.
18. Schultz NH, Sorvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021 Apr 9 [Epub]. <https://doi.org/10.1056/NEJMoa2104882>.
19. Muster V, Gary T, Raggam RB, et al. Pulmonary embolism and thrombocytopenia following ChAdOx1 vaccination. *Lancet* 2021;397:1842.
20. Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021 Apr 16 [Epub]. <https://doi.org/10.1056/NEJMoa2105385>.
21. Krakow EF, Goudar R, Petzold E, et al. Influence of sample collection and storage on the detection of platelet factor 4-heparin antibodies. *Am J Clin Pathol* 2007;128:150-5.
22. Greinacher A, Selleng K, Wesche J, et al. Towards understanding ChAdOx1 nCov-19 Vaccine-induced immune thrombotic thrombocytopenia (VITT). Preprint at <https://doi.org/10.21203/rs.3.rs-440461/v1> (2021).