CASE REPORT

# A RARE CASE OF SUBCONJUNCTIVAL HEMORRHAGE POST COVID-19 mRNA VACCINE: A CASE REPORT

**Jovita Jutamulia[1], Arlin Chyntia Dewi[2], Salma Salsabila[3], Vicky Octaviani[1]**
*[1]Faculty of Medicine, Trisakti University, Jakarta, Indonesia*
*[2] Faculty of Medicine, YARSI University, Jakarta, Indonesia*
*[3]Faculty of Medicine, Diponegoro University, Semarang, Indonesia*
*Email: jovita.jutamulia@gmail.com*

## ABSTRACT

***Introduction:*** *Concurrently with the administration of COVID-19 vaccine, adverse event following immunization (AEFI) began to be reported. Some reactions involve various systems of the human body, including the ocular system. Although uncommon, subconjunctival hemorrhage also can be found, as shown in this report.*

***Case Report:*** *We present a case of a 68-year-old woman with subconjunctival hemorrhage a couple hours before admission. Patient also came with complaints of sudden redness and pain in left eye. Two days prior, she had her first dose of COVID-19 mRNA vaccine. Left eye examination revealed hemorrhage on conjunctiva with normal visual acuity. Other ocular examinations couldn't be done due to the lack of facilities and severe pain. No other symptoms were mentioned. Patient was advised to be referred to an ophthalmologist, but she refused. After a month, the patient reportedly experienced similar complaints after receiving the second dose of COVID-19 mRNA vaccine. another redness and discomfort in her left eye. Her left eye was red, itched, and swollen. However, she still refused to go to an ophthalmologist. Oral analgesic, oral antihistamine, and artificial tears were given. The symptoms were completely resolved in a couple days.*

***Conclusion:*** *Subconjunctival hemorrhage may occur as mRNA Vaccine AEFI specifically in patients with underlying disease, however further research is needed.*

***Keywords:*** *subconjunctival hemorrhage, AEFI, COVID-19, mRNA vaccine*

## INTRODUCTION

On March 11, 2020, WHO declared the novel coronavirus (COVID-19) outbreak a pandemic.[1] With its contagiousness and rapid spread, COVID-19 vaccines bring rays of hope to face this pandemic. The first COVID-19 vaccine outside a clinical trial setting was administered on Dec 8, 2020.[2] There are many types of COVID-19 vaccines currently available with different approaches. Those are the whole microbe approach (inactivated vaccine, live-attenuated vaccine and viral vector vaccine), protein subunit approach, and genetic approach (Messenger RNA (mRNA) vaccine).

On December 18, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the Moderna COVID-19 (mRNA-1273) vaccine, a lipid nanoparticle-encapsulated, nucleoside-modified mRNA vaccine encoding the stabilized prefusion spike glycoprotein of SARS-CoV-2, the virus that causes coronavirus disease 2019.[3] Sahly et al mentioned that Moderna vaccine efficacy in preventing COVID-19 illness was

93.2%.[4] Latest study by Self et al compared 3 COVID-19 vaccines (Moderna, Pfizer-BioNTech and Janssen) and showed that after 2 dose regimens, vaccine effectiveness (VE) against COVID-19 hospitalization for Moderna and Pfizer-BioNTech vaccines, both mRNA vaccines, was 93% and 88%, respectively, whereas the single-dose Janssen vaccine, a viral vector vaccine, had somewhat lower VE at 71%.[5]

Despite its efficacy and effectiveness, some adverse reactions were reported post-COVID-19 vaccinations along its global administration. Some reactions involve various systems of the human body, including the ocular system. Some of the most common reported Ocular Adverse Event Following Immunization (AEFI) are blurred vision, eye swelling, followed by eye pain and visual impairment.[6] Although uncommon, subconjunctival hemorrhage (SCH) also can be found, as also shown in this report. Here, we report a rare case of an Ocular AEFI post mRNA-1273 COVID-19 vaccine injection.

## CASE ILUSTRATION

A 68-year-old woman came to outpatient clinic with complained of redness and pain in her left eye a couple of hours before admission to our clinic. Both symptoms suddenly appeared when she was resting. The patient denied a history of headache, nausea, vomiting, double vision, and pain when moving the eyeballs. Two days prior, she had her first dose of mRNA-1273 COVID-19 vaccine, Moderna vaccine. She had a history of hypertension and consumed anticoagulant and hypertension medicine routinely. She had no history of ocular and systemic disease, ocular trauma, straining, chronic cough, heavy lifting, and severe sneezing prior to complaints.

Her vital status showed an increased blood pressure of 150/90 mmHg, while other vital status was normal. For the ocular examination, her left eye revealed diffuse hemorrhage on conjunctiva with visual acuity of 6/6. Chemosis was present in the conjunctiva of her left eye. The right eye examination was normal. Other ocular examinations couldn't be done due to the lack of facilities and severe pain. Laboratory workup also could not be done because of the similar reason. Because of the mentioned limitations, the patient was advised to be referred to an ophthalmologist, however she refused. As for the medications, we prescribed her artificial tears 4 times daily, oral mefenamic acid three times daily, and suggested resting in a semi-Fowler position.

One month later, she came with redness and discomfort in her left eye. Her left eye was red, itched, and superior palpebra looked swollen. Her visual acuity remained normal (6/6). The right eye examination was normal. She had her second dose of mRNA-1273 COVID-19 vaccine

two days ago. She had no trauma, ocular and systemic disease prior to these complaints. However, she still refused to be referred to the ophthalmologist. Oral cetirizine once daily and artificial tears 4 times daily were given. She came for a follow-up in a couple of days and showed all symptoms were completely resolved with normal visual acuity in both eyes.

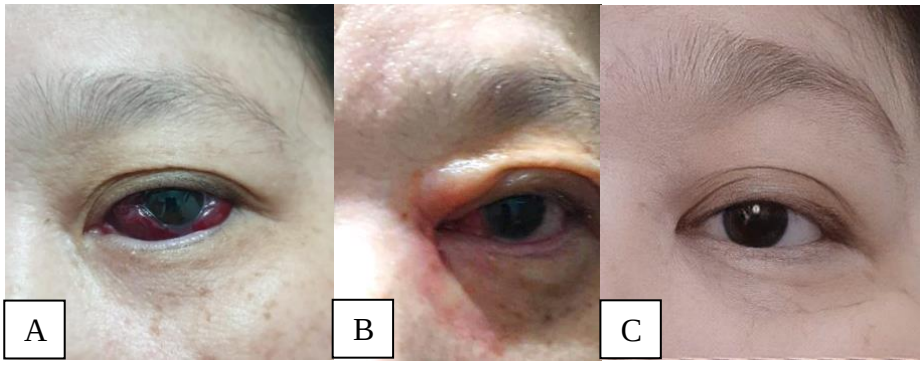


**Figure 1.** Clinical presentation (A) first visit (after first dose of mRNA-1273 COVID-19 vaccine), (B) second visit (after second dose of mRNA-1273 COVID-19 vaccine), (C) third visit (follow-up after second visit)

## DISCUSSION

Subconjunctival hemorrhage (SCH) is a common benign condition of the eye that is caused by the rupture of a conjunctival vessel, resulting in local extravasation of blood into the subconjunctival tissue and subconjunctival episcleral space. It is generally painless with acute appearance of a sharply circumscribed redness or diffusely hyperemic bleeding underneath the conjunctiva in the absence of discharge and inflammation in contagious areas.[7-9] It can vary from dot-blot hemorrhages to extensive areas of bleeding.[8] Reduction in visual acuity is not expected.[7-9] The initially red hemorrhage turns orange and yellow when blood degradation and absorption take place, with absorption usually being complete four to seven days after the hemorrhage.[7]

Subconjunctival hemorrhage can be differentiated into two categories, traumatic and spontaneous, and the majority of cases are spontaneous.[7-9] The first study on the risk factors was reported by Fukuyama et al in 1990, who showed that local trauma, systemic hypertension, acute conjunctivitis, and diabetes mellitus were the main causes or associated conditions of SCH.[8,10] Hypertension has been shown to be the major risk factor for SCH regardless of whether the blood pressure is controlled by medication. These diseases can cause blood vessels to become fragile and spontaneously rupture. Anticoagulants and P2Y12 inhibitors such as clopidogrel can also increase the risk for SCH.[9] It is consistent with our patient; she had a history of hypertension and consumed anticoagulant and hypertension medicine routinely.

Aside of that, along with global administration of COVID-19 vaccine, SCH cases were reported as AEFI COVID-19 vaccine.

In general, some of the most common AEFI were localized pain in the injection site, malaise, fatigue, and headache.[4,12] Specifically, ocular AEFI also has been reported, such as blurred vision, eye swelling, eye pain and mild visual impairment.[6,13] Although it is uncommon, SCH, had been reported as an ocular AEFI post mRNA-1273 COVID-19 vaccine. Researchers from Administrative Data Research United Kingdom has found 634 ocular AEFI cases after mRNA-1273 vaccine administration and 3 of them were subconjunctival hemorrhage.[11]

The mRNA vaccine has been utilized as therapeutic and research tools for more than two decades, with the usage ranging from *in vitro* transcribed (IVT) mRNA, small interference RNA (siRNA), RNA aptamers, riboswitches, et cetera.[14] The RNA vaccine contains messenger RNA (mRNA), which contains an instruction to make a SARS-CoV-2-spike protein. The mRNA molecules can be directly delivered into immune cells for manipulating gene expression or producing protein spike. The spike protein produced by the mRNA-based vaccines may serve as a trigger by itself or by inducing an immunological response. Molecular mimicry between the spike protein and a self-antigen could stimulate platelet activation and ocular haemorrhage.[14,15]

Systemic conditions like hypertension, diabetes mellitus, arteriosclerosis, can lead to localized blood vessel abnormality. The eyes that more vulnerable to microvascular dysfunction are also more likely to develop haemorrhagic complications after SARS-CoV-2 vaccination.[14,15] Hyo Song Park, et al reported that more than 80% of the patients (17 of 21) that experience eye bleeding after given mRNA COVID-19 vaccination had diabetes or hypertension.[15] The fact that our patient has hypertension for over the years, puts her in the high-risk condition.

Another possible cause of SCH after vaccination is called vaccine-induced thrombotic thrombocytopenia (VITT).[16] In this condition, patients appear to have platelet factor 4 antibodies (anti-PF4 Ab), which mimic the effects of heparin by binding to a similar site on PF4 and allowing PF4 to cluster into immune complexes that cause Fcγ receptor IIa-dependent platelet activation. This condition can be exacerbated if the patient is taking antiplatelet drugs. The mechanisms by which these conditions develop are still unknown.[16,17] Unfortunately, the patient had not done any laboratory examination to exclude this cause.

In general, SCH does not need any therapy unless it is linked to a significant condition. Depending on the volume of extravasated blood, the blood is generally reabsorbed over 1-2 weeks. If a patient is consuming anticoagulant, recovery could take up to 3 weeks. To reduce

tissue swelling and alleviate discomfort, ice packs and artificial tears can be used to relieve each symptoms, respectively. The use of nonsteroidal anti-inflammatory drugs can be considered. Intravitreal injections, oxymetazoline and diluted brimonidine have increased patient comfort and reduced incidence of SCH. Patient with underlying systemic cause should have treatment directed to their condition.[9] We prescribed the patient with artificial tears 4 times daily, oral mefenamic acid three times daily, and suggested resting in a semi-Fowler position to improve her condition.

After resolution, SCH provides a fair visual prognosis. In most cases, vision is not hampered. Without observable risk factors, the recurrence probability for spontaneous SCH is around 10%, which rises if patients receive anticoagulant or antiplatelet therapy.[9] As we prescribed patient with treatments given above and also the discontinuation of anticoagulants, patient still experienced the exacerbation of the same AEFI on her second dose of vaccination. We informed the patient to come back after 1 week for further follow up on her first visit. Unfortunately, the patient did not come back, thus further evaluation of patient's condition could not be done. On her second visit concerning the exacerbation, the patient came for a follow up after a couple of days. All symptoms were completely resolved with normal visual acuity in both eyes.

This report still has some limitations. Due to the limited facilities at the clinic and the severe pain, it was hard to examine the patient's eye thoroughly. The reluctance of the patient being referred to the ophthalmologist also made it difficult for us to find the precise diagnosis.

## CONCLUSION

Eventhough it is uncommon, subconjunctival hemorrhage should be noted as one of the AEFI of mRNA-1273 COVID-19 vaccine. This AEFI may occur in patients with underlying disease and in anticoagulant treatment. Further researches regarding subconjunctival hemorrhage as the AEFI of the COVID-19 vaccines are needed.

## REFERENCES

1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020;91(1):157–60
2. Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. Lancet Infect Dis. 2022; 22: 1293–302
3. Oliver SE, Gargano JW, Marin M, Wallace M, Curran KG, Chamberland M, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine - United States, December 2020. MMWR Morb Mortal Wkly Rep. 2021;69(5152):1653–6.
4. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med. 2021;385(19):1774–85.
5. Self WH, Tenforde MW, Rhoads JP, Gaglani M, Ginde AA, Douin DJ, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(38):1337-1343

6. Sodhi M, Etminan M. Reported ocular adverse events with three COVID-19 vaccines. Acta Ophthalmol. 2022;100(7):e1537-e1538.
7. Hu D-N, Mou C-H, Chao S-C, Lin C-Y, Nien C-W, Kuan P-T, et al. Incidence of Non-Traumatic Subconjunctival Hemorrhage in a Nationwide Study in Taiwan from 2000 to 2011. PLoS ONE. 2015; 10(7): e0132762
8. Tarlan B, Kiratli H. Subconjunctival hemorrhage: risk factors and potential indicators. Clinical Ophthalmology. 2013;7: 1163–1170
9. Doshi R, Noohani T. Subconjunctival Hemorrhage [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [updated 2022 Feb 23; cited 2022 Sep 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551666/
10. Fukuyama J-I, Hayasaka S, Yamada K, Setogawa T. Causes of Subconjunctival Hemorrhage. Ophthalmologica. 1990; 200:63-67
11. Medicine and Healthcare Product Regulatory Agency (GB). COVID-19 Moderna Vaccine Analysis Print [Internet]. London: Medicine and Healthcare Product Regulatory Agency; 2022 [updated 2022 Aug 25, cited 2022 Sep 10]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1101772/Vaccine_Analysis_Print_Moderna_COVID-19_vaccine_24.08.2022.pdf
12. Supangat, Sakinah EN, Nugraha MY, Qodar TS, Mulyono BW, Tohari AI. COVID-19 Vaccines Programs: adverse events following immunization (AEFI) among medical Clerkship Student in Jember, Indonesia. BMC Pharmacology and Toxicology. 2021;22:58
13. Testi I, Brandão-de-Resende C, Agrawal R, Pavesio C, COVID-19 Vaccination Ocular Inflammatory Events Study Group. Ocular inflammatory events following COVID-19 vaccination: a multinational case series. J Ophthalmic Inflamm Infect. 2022;12(1):4
14. Park J, Lagniton P, Liu Y, Xu R. mRNA vaccines for COVID-19: what, why and how. International Journal of Biological Sciences. 2021;17(6):1446-1460.
15. Park H, Byun Y, Byeon S, Kim S, Kim Y, Lee C. Retinal Hemorrhage after SARS-CoV-2 Vaccination. Journal of Clinical Medicine. 2021;10(23):5705.
16. Ng X le, Betzler BK, Ng S, Chee SP, Rajamani L, Singhal A, et al. The eye of the storm: COVID-19 vaccination and the eye. Ophthalmol Ther. 2021;1–20.
17. Amin MA, Nahin S, Dola TA, Afrin S, Hawlader MDH. Retinal hemorrhage of late post-COVID-19 and post-vaccine-related pathogenic mechanisms: A new challenge for ophthalmologist in COVID era. Clin Case Rep. 2022;10(2):e05471.
18. Sodhi PK, Jose R. Subconjunctival hemorrhage: the first presenting clinical feature of idiopathic thrombocytopenic purpura. Jpn J Ophthalmol. 2003;47(3):316–8.