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CASE REPORT

Delayed Localized Hypersensitivity Reactions to an Adenoviral Vector Vaccine—A Literature Review and a Case Report with Serial Ultrasonography Follow-up

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Abstract

Severe acute respiratory syndrome coronavirus 2 has changed our life worldwide. Vaccination plays an important role in this pandemic to reduce virus transmission and lower the mortality risk. However, as vaccination rates increase, so do the reported adverse effects. This report describes a case of 28-year-old female with severe subcutaneous swelling persisting almost 1 month after receiving the recombinant adenoviral vector vaccine (ChAdOx1 nCov-19, AZD1222), despite paracetamol prophylaxis. The ultrasonography showed a hyperechoic swelling in the subcutaneous layer and a diffuse hypoechoic muscle layer. The phenomenon results from delayed hypersensitivity, however, its clinical picture is often confused with cellulitis and abscess. Ultrasonography is a real-time and convenient diagnostic tool to help clinical practitioners determine the differential diagnoses.

Keywords: Adenoviral vector vaccine, Ultrasonography, Delayed localized hypersensitivity

1. Introduction

Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became a pandemic in 2020, the disease has caused more than 4 million deaths.¹ The SARS-CoV-2 vaccination played an important role in reducing virus transmission and preventing severe symptoms.^{2–4} The ChAdOx1 nCoV-19 (AZD1222) vaccine was one of the SARS-CoV-2 vaccines using a modified adenovirus as a vector.⁵ World Health Organization (WHO) suggested two doses of AZD1222 administration with a 12-week dose interval.⁶ To reach maximal protection, accumulated evidence recommended to

receive one more Messenger RNA (mRNA) vaccine 80 days after the second AZD1222 injection.⁷

Common adverse effects of ChAdOx1 nCoV-19 vaccine are fever, chills, headache, and general myalgia.⁵ Symptom severity and intensity are higher after the first shot, especially in the first 3 days post-vaccination.⁵ Rare but well-known adverse effects are embolic events or thrombosis with thrombocytopenia syndrome.⁸ Localized swelling, pain, and induration are predictable symptoms caused by intramuscular injection.⁵ In the ChAdOx1 nCoV-19 vaccine phase 1 and 2 vaccine study, a localized reaction with induration and/or erythema

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diameter of less than 2.5 cm was acceptable and not considered an adverse effect.⁵ Very few cases experienced moderate to severe local swelling (2%) and induration (<1%).⁵ No participant taking prophylactic paracetamol reported induration post-vaccination.⁵

A literature review showed no reports of severe long-term subcutaneous skin reaction after ChAdOx1 nCoV-19 vaccination with prophylactic paracetamol. This case report presents a patient who had a severe local reaction after the first dose of the ChAdOx1 nCoV-19 vaccine despite receiving prophylactic paracetamol.

2. Case report

A 28-year-old woman without chronic or hereditary disease and allergic or recent traumatic history received her first dose of the ChAdOx1 nCoV-19 vaccine on May 17, 2021. Before vaccination, the patient took one prophylactic dose of paracetamol (500 mg). Several hours post-vaccination, she experienced mild fever (37.5 °C), headache, chills, generalized bone pain, myalgia, and fatigue. To alleviate intolerable myalgia and pain, she took paracetamol (500 mg) and ibuprofen (400 mg) every 4 h for the first 3 days, and her systemic symptoms resolved on post-vaccination Day 3. However, on post-vaccination Day 2, she noted redness, swelling, and pain in the injection area of her left lateral arm. The swelling and induration progressed to spread over her arm, and severe pain limited her arm elevation.

Physical examination in the outpatient clinic showed a large area of erythema, tenderness, and swelling of the soft tissue

mass without pus formation (Fig. 1). For further diagnosis, the patient was transferred for ultrasonography on post-vaccination Day 4.

The patient underwent ultrasonography using a Voluson 730 Expert (General Electric Medical Systems Kretztechnik, Zipf, Austria) ultrasound machine with a 6–12-MHZ linear-array transducer. Ultrasonography revealed a large area (length, width, and height up to 6.61 × 9.32 × 1.90 cm) of hyperechoic swelling (volume 61.25 cm³) in the subcutaneous layer (Fig. 2A). Repeat ultrasonography on June 4, 2021, post-vaccination Day 18, showed significantly decreased area of subcutaneous swelling (3.46 × 4.38 × 1.33 cm) (Fig. 2B) with volume decreased to 10.54 cm³ (82.79% reduction of swelling). Repeat ultrasonography on June 18, 2021, post-vaccination Day 32, showed an additional decrease in size to 2.52 × 4.27 × 1.17 cm and volume to 6.58 cm³ (Fig. 2C). Compared with the second ultrasound, the volume on the third ultrasound was a 62% reduction. The sonography series revealed that the deltoid muscle layer had lost the starry-night pattern (Fig. 2).

Power Doppler examination revealed diffused high-color-gain signals in the muscle layer; however, the color flash artifact was suspected instead of increased vascularization (Fig. 3). Neither solid cellulitis nor abscess formation was evident. Compared with the patient's healthy arm, which had a smooth and homogenous subcutaneous and muscle layer, the vaccination arm showed a prominent hyperechoic change in the subcutaneous layer with a



Fig. 1. A large area of induration spreads over the left deltoid region with extensive erythema, photographed on the post-vaccination Day 4.

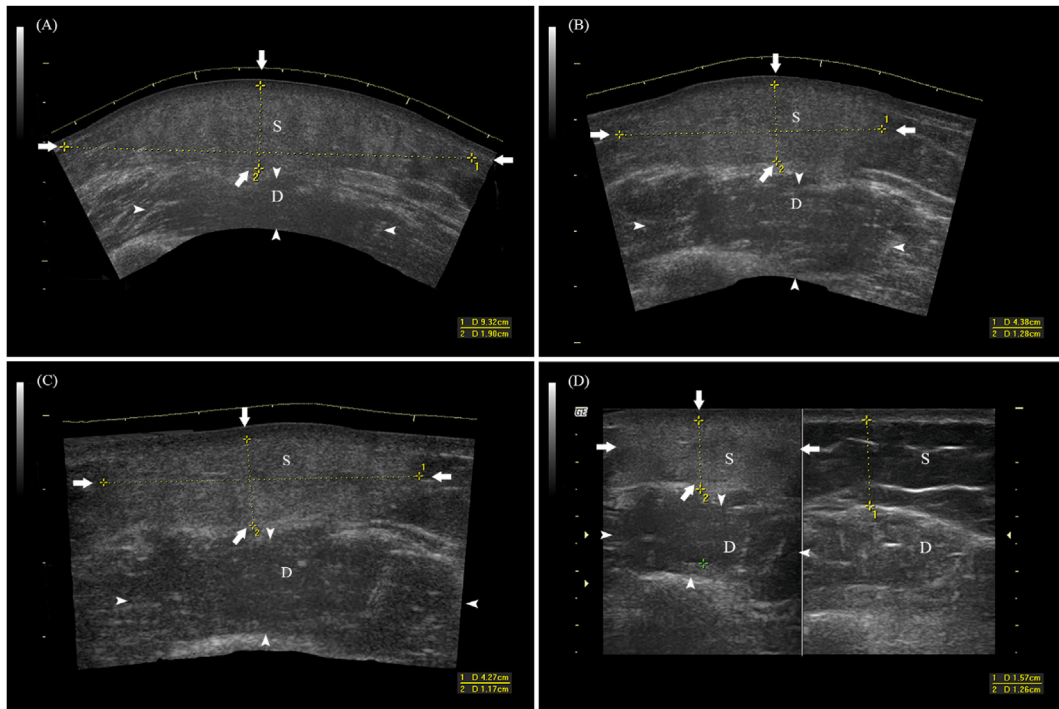


Fig. 2. Ultrasonography shows an induration in the subcutaneous layer with a diffuse hypoechoic muscle layer after vaccination on the left arm in transverse plane (A), on post-vaccination Day 4 (05/21/2021). (B), on post-vaccination Day 18 (April 06, 2021). (C), and on post-vaccination Day 32 (06/18/2021). (D), comparison of bilateral upper arms—right upper arm shows a normal subcutaneous layer and muscle layer, whereas the left upper arm shows a prominent hyperechoic change in the subcutaneous layer and hypoechoic change in the muscle layer on post-vaccination Day 32 (06/18/2021). The white arrow indicates the lesion in the subcutaneous layer. The arrowhead indicates the lesion in the muscle layer. (S: Subcutaneous layer; D: Deltoid muscle layer).

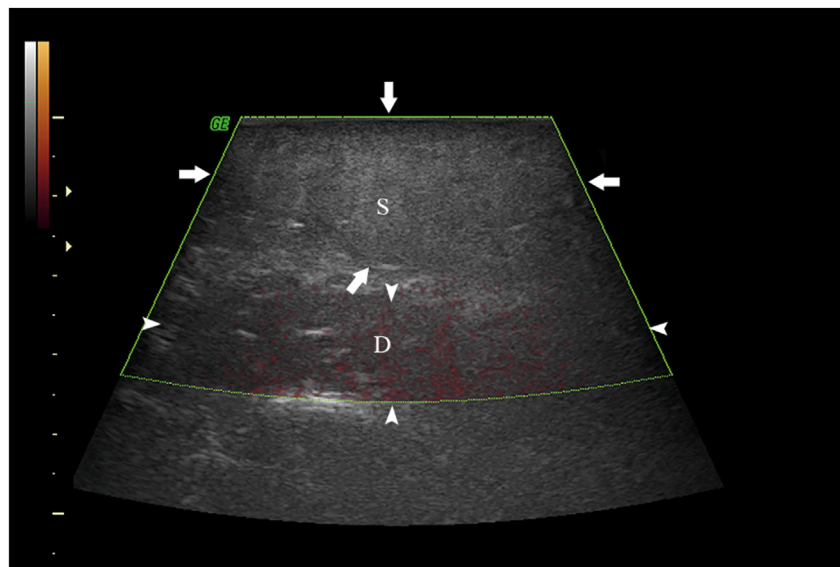


Fig. 3. Power Doppler ultrasonography shows no increased blood flow in the subcutaneous layer with a mildly increased signal in the muscle layer on postvaccination Day 4 (05/21/2021). The white arrow indicates the lesion in the subcutaneous layer. The arrowhead indicates the lesion in the muscle layer. (S, subcutaneous layer; D, deltoid muscle layer).

diffuse hypoechoic change in the muscle layer (Fig. 2D).

3. Discussion

The incidence of moderate to severe local skin reaction after ChAdOx1 nCoV-19 vaccine is rare.⁵ Based on previous trials, the skin reaction can be reduced or prevented by prophylactic paracetamol.⁵ In ChAdOx1 nCoV-19 vaccine phase 1 and 2 trials, the incidence of moderate to severe localized induration was 0.6% without prophylactic paracetamol versus 0% with prophylaxis.⁵ Based on the phase 1 and 2 studies, the degree of the local skin reaction in our case can be defined as moderate to severe induration, swelling, and erythema.⁵ Such an extensive degree of localized skin reaction rarely occurs with prophylactic paracetamol.⁵

Potential mechanisms for the subcutaneous and muscle swelling include delayed hypersensitivity reactions, bruise or blunt trauma, and incorrect vaccination route. Lindgren et al. reported that COVID-19 vaccine ingredients, including polyethylene glycol 2000 and polysorbate 80, may lead to delayed hypersensitivity.⁹ The ChAdOx1 nCoV-19 vaccine also uses polysorbate 80 as an excipient.⁸ Therefore, delayed hypersensitivity may have led to the subcutaneous swelling. Further, according to the package insert, intramuscular injection is the only suggested administration route for ChAdOx1 nCoV-19 vaccine.¹⁰ One review demonstrated that subcutaneous vaccine administration increases the risk of a skin adverse reaction and deteriorates the immunologic vaccine benefit.¹¹ Use of a longer needle, at least 25 mm, is recommended to prevent an error in the administration technique.^{11–13} In our case, because the patient underwent the standard intramuscular injection procedure, the possibility of an incorrect vaccination route was low. Moreover, although blunt trauma and bruises present with a thick and hyperechoic subcutaneous layer, the clinical picture of the patient in this report makes this impression less likely. First, the patient had no trauma history, except for vaccination. Second, according to previous studies, bruises mostly resolve within 2 weeks.^{14,15} The patient in this report suffered from the

lesion for more than 1 month. Moreover, Chambers et al.¹⁶ have noted that the subcutaneous layer could progress to fat necrosis in blunt trauma. Fat necrosis is a hypoechoic halo surrounded by ill-defined hyperechoic or isoechoic lesions,¹⁶ which was absent in our sonography series. Therefore, we believe that the patient had delayed hypersensitivity reactions, resulting in angioedema, which led to subcutaneous and muscle swelling.

A vaccination-related delayed skin response is not limited to the ChAdOx1 nCoV-19 vaccine; similar phenomenon are reported for the COVID-19 vaccines from both mRNA-1273 (Moderna) and BNT162b2 (BioNTech/Pfizer),^{9,17} with the symptoms of a large area of erythema, warmth, swelling, and induration, typically occurring 7 days post-vaccination.¹⁷ However, recovery was not delayed for any of the reported cases for more than 1 month.^{9,17} Topical corticosteroids were selectively used for such cases, which could be the reason why swelling reduced rapidly.¹⁷ In our case, the patient only took an oral anti-inflammatory agent for the first 3 days to relieve systemic symptoms and no other oral or topical medications for her swelling arm, which may have resulted in the longer course of localized skin symptoms.

It is difficult to distinguish the nature of this skin reaction from cellulitis or early abscess in the clinical setting. Lindgren reported several skin reaction cases that were misdiagnosed with cellulitis.⁹ The clinical presentation of cellulitis and early abscess was similar to the presentation in our case: progressive swelling, erythema, warmth, and tenderness.¹⁸ The injection procedure itself also created a risk of cellulitis because of skin barrier destruction.¹⁸ Without early management, the local infection may lead to severe systemic infection, especially in immunocompromised patients.^{18,19} Ultrasonography is a convenient, accurate, and real-time diagnostic tool. Both the sensitivity and specificity of ultrasonography for detecting cutaneous abscesses can reach 80%.²⁰ Cellulitis shows a cobblestone appearance in the subcutaneous layer with fluid accumulation (Fig. 4).^{21,22} Abscesses may be surrounded by cellulitis, with a characteristic irregular and anechoic cavity and hyperechoic posterior acoustic

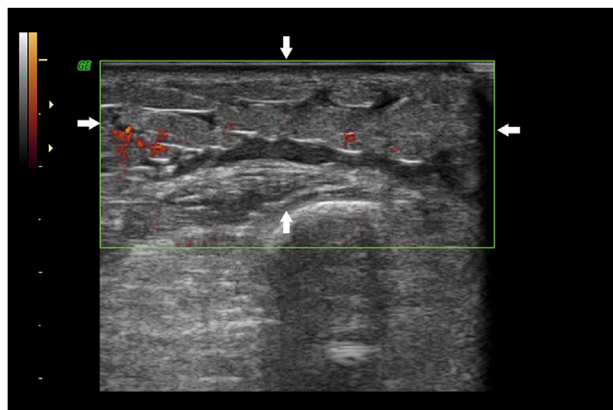


Fig. 4. A 67-year-old woman with cellulitis at the right forearm. Ultrasonography demonstrates a cobblestone pattern with fluid accumulation (white arrow) over the subcutaneous layer. Power Doppler reveals hyperemia.

enhancement.²¹ However, the cobblestone pattern may also be observed in noninfectious causes of tissue edema.²³ Clinicians can use Power Doppler to distinguish this condition from others; the signals are increased because of vascularization in cellulitis and abscess.^{21–23} Otherwise, if an abscess were highly suspected, ultrasound-guided aspiration could be performed and the pus formation could be drained. In our case, we could easily differentiate the subcutaneous swelling response from cellulitis and even an abscess. Furthermore, ultrasonography is a convenient tool for serial follow-up to prevent other complications.

Fortunately, individuals who experienced a skin reaction from the initial ChAdOx1 nCoV-19 vaccine are still able to receive the further booster dose. The only contraindication to the ChAdOx1 nCoV-19 vaccine listed in WHO interim guidance is an anaphylactic reaction post-vaccination.⁶ Despite possible severe local reaction, the skin reaction is self-limited, and the recovery can be accelerated by topical corticosteroids. Furthermore, McMahon reported a lower risk of delayed skin reactions on the second dose of COVID-19 vaccine from both mRNA-1273 and BNT162b2.¹⁷ Because SARS-CoV-2 infection may be life-threatening, the benefit of the vaccination outweighs the risk of a delayed local reactions.

4. Conclusion

Delayed hypersensitivity that causes a severe skin reaction is an uncommon adverse effect of the ChAdOx1 nCoV-19

vaccine. Swelling and induration are self-limited, and the second boost of vaccination is still recommended. For clinicians, it is important to identify carefully delayed hypersensitivity because the signs are similar to cellulitis and early abscess. In our case, ultrasonography revealed an increased thickness in the subcutaneous layer and the muscle layer without evidence of hyperemia, which is characteristic of angioedema. Ultrasonography plays an important role in convenient and accurate early diagnosis and serial follow-up to prevent further complications of vaccination.

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Declaration of Conflicting Interest

The authors declare that there is no conflict of interest.

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None.

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