CASE REPORT

Case Report: Adult Onset Still’s Disease after vaccination against Covid-19 [version 2; peer review: 2 approved]

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Abstract
Vaccination against the virus responsible for COVID-19 has become key in preventing mortality and morbidity related to the infection. Studies have shown that the benefits of vaccination outweigh the risks. However, there are concerns regarding serious adverse events of some vaccines, although they are fortunately rare. Here, we report a case of a 47-year-old female from Kathmandu who presented with high grade fever, dry cough and erythematous rash a week after exposure to the Oxford-AstraZeneca vaccine. She had hepatosplenomegaly, persistent leucocytosis, anaemia and thrombocytosis along with markedly raised inflammatory markers. Her tests for infectious causes and haematological malignancies were negative and she showed no response to multiple antibiotics. Finally, she had a dramatic response to steroids with disappearance of fever and normalization of other laboratory parameters. Hence, she was diagnosed with Adult-onset Still’s Disease (AOSD). She was under methotrexate and prednisolone tapering dose and doing well as of the time of writing. The trigger for the disease was hypothesized to be the vaccine because of the strong temporal association.

Keywords
Covid-19 vaccination, AOSD
Introduction
COVID-19 is a major pandemic currently affecting the whole world, and Nepal is no exception. As of 31 March 2022, a total of 978,402 people had been infected and 11,951 people have already lost their lives in Nepal. However, various vaccines have been tested and made available which are highly effective in preventing both the morbidity and mortality associated with the disease. However, there are concerns regarding adverse events following vaccination. Adult-onset Still’s Disease (AOSD) is a multisystem auto-inflammatory disease characterized by high grade fever, inflammatory arthritis, and an evanescent rash. It is associated with profound systemic inflammation marked by high inflammatory markers, leucocytosis and high ferritin levels. The diagnosis is made clinically after ruling out other aetiologies. We describe a case of AOSD following administration of the Oxford-AstraZeneca vaccine in Nepal. AOSD is a rare autoinflammatory disease and diagnosis of this case itself is a challenge, especially in a country like Nepal, where rheumatology is a budding speciality. This case follows only two other similar reported cases after vaccination against COVID-19.

Case presentation
A 47-year-old female from Kathmandu, Nepal, non-smoker presented in April 2021 to the out-patient department of a tertiary hospital in Kathmandu, with a history of intermittent fever and sore throat for nine days. After three days of fever, she developed itchy erythematous rashes bilaterally involving thighs, legs and hands, especially during the spiking of fever. She had received the first dose of the Oxford-AstraZeneca vaccine seven days prior to the onset of fever. She had no notable past medical and family history. When she presented to us, she was already on two antibiotics, namely levofloxacin 750 mg and azithromycin 500 mg, once daily for a couple of days from a local medical shop. Upon examination, her temperature was 38.5°C, and had erythematous rashes over bilateral legs and hands (Figure 1). The remaining systematic examination found no further anomalies. SARS-CoV-2 polymerase chain reaction (PCR) was negative. The initial laboratory investigations (Table 1) showed anaemia with neutrophilic leucocytosis and thrombocytosis, raised C-reactive protein (CRP), markedly raised ferritin, and mild hepatitis. Ultrasound of the abdomen showed hepatosplenomegaly. She was admitted with intravenous ceftriaxone 2 g once daily and oral doxycycline 100 mg twice daily. Blood and urine cultures were performed, which later revealed no growth. Serological tests for dengue, scrub typhus, leptospirosis and malaria were negative. There was no response to antibiotics after 72 hours. Further investigations were performed considering possible non-infectious causes of fever. Her antinuclear antibody (ANA) was weakly positive with a fine speckled pattern. Rheumatoid factor, anti-citrullinated peptide antibodies (ACPA), and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Her bone marrow cytology was normal. On the fourth day of her admission, she also developed pain and swelling of her left elbow. On examination, the elbow joint was warm and tender with restriction of movement. At this time, AOSD was considered as the most probable diagnosis since she fulfilled three major and three minor criteria as defined by Yamaguchi. She was then started on prednisolone at 1 mg/kg (60 mg) once daily, with continuation of the ongoing antibiotics. After starting prednisolone, she had no further episodes of fever. Her joint pain improved, and she experienced no further rash. Thus the final diagnosis of AOSD was made based on the classification criteria and a dramatic response to the steroid. Methotrexate 7.5 mg per week was started. The antibiotics were stopped on the seventh day, and she was discharged with prednisolone and methotrexate. She is under regular follow-up for her condition at the time of writing this report. During her latest follow-up in September 2021, she was afebrile and had no other symptoms. She is currently receiving prednisolone 10 mg daily and methotrexate 15 mg per week. She has not received any further dose of the vaccination.

Discussion
Vaccination against COVID-19 has become the most effective way to curb the current pandemic and its effects on activities...
worldwide. As of the time of writing this report, several vaccines had undergone trials and been given approval to be rolled out in several countries. Minor side effects after vaccination are fairly common; however, there have been some concerns regarding rare but serious adverse events of some vaccines. For example, cerebral venous sinus thrombosis has been described in some patients who have received the Ad26.COV2.S (Janssen/Johnson & Johnson) COVID-19 vaccine. Likewise, several cases of thrombosis have developed following vaccination with the Oxford-AstraZeneca vaccine. Autoimmune diseases themselves are rare, and those developing following vaccination are even rarer. Recently some cases of autoimmune diseases following COVID-19 vaccination have been described.

Adult-onset Still’s disease (AOSD) is a rare auto-inflammatory disorder characterized by a high spiking fever, arthralgia (with or without synovitis), maculo-papular salmon-pink evanescent skin rash, striking leucocytosis with neutrophilia. There is no definitive confirmatory test for AOSD, but there are a few sets of clinical criteria which are used in the diagnosis. In one study in France, the incidence of the disease was found to be 0.16 per 100,000 in the population. The aetiology of the disease is unknown. Various genetic and environmental factors have been implicated in the causation of the disease, but there is no definite evidence. The pathogenesis involves activation of the innate immune system with subsequent cytokine overproduction, especially interleukins IL-1 and IL-6, TNF-α, and IFN-γ. Several infectious agents have been postulated to trigger the disease in genetically predisposed individuals. It has been proposed that the interplay between host genetic factors, autoimmune mechanisms, and antigens could trigger AOSD. There have been some case reports of AOSD following a COVID-19 infection in patients who had recently recovered from the illness. However, only one case of AOSD has been reported following vaccination with the mRNA-1273 COVID-19 vaccine (Moderna), and one after ChAdOx1 nCoV-V-19 (Oxford-AstraZeneca) vaccine. There are two possible ways the vaccine could have triggered the disease; one is through the release of various cytokines by the spike protein and the other is the activation of the immune system by the adenovirus vector used in the vaccine. It is well-known from various studies that COVID-19 infection causes a release of various cytokines and multi-organ failure (secondary hemophagocytic lymphohistiocytosis). The main cytokines with elevated levels in this condition are IL-1 and IL-6, which are the same cytokines that are activated in AOSD, which points towards a similar mechanism of immune activation. As in AOSD, IL-1 and IL-6 blockade has been successful in the management of patients with severe COVID-19 infection. The Oxford-AstraZeneca vaccine is based on a replication-incompetent chimpanzee adenovirus vector that expresses the SARS-CoV-2 spike protein. Many cases of viral infections, including by adenoviruses, have been reported to trigger AOSD. It is possible that the adenovirus vector used in the vaccine could have triggered the same mechanism as that triggered by the native virus. However, the level of SARS-CoV-2 anti-spike protein IgG in the serum could not be performed which could have shown some light regarding the possible pathogenesis in our patient. Whatever the pathogenesis, the strong temporal association between the vaccination and the onset of symptoms made us suspect the vaccine to be the trigger, although it could be mere coincidence. Further studies are needed to prove the causation.

### Conclusions

AOSD is a rare disease that has been associated with environmental triggers in genetically susceptible hosts. Vaccination against COVID-19 could be a potential trigger for its development for which further studies are required.

### Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

### Data availability

All data underlying the results are available as part of the article and no additional source data are required.
Open Peer Review

Current Peer Review Status: ✔️ ✔️

Version 2

Reviewer Report 22 August 2022

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✔️ Sankha S. Chakrabarti
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Acceptable, but I could not access the supplementary file of causality assessment. Please ensure it is added.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Geriatric pharmacovigilance, Geriatric neuropsychiatry, COVID-19 (vaccines)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 21 March 2022

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❓ Sankha S. Chakrabarti
Department of Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

This is an interesting and well managed case.
1. Kindly update the case and death numbers in Nepal to March 2022 figures

2. English language editing is much needed to improve clarity, in the Abstract, Introduction and Case Presentation parts.

3. Use the word hepatitis instead of transaminitis.

4. Use bone marrow cytology (or histopathological examination of bone marrow biopsy sample) whichever is suitable, instead of histopathological bone marrow examination.

5. Please mention the consideration made by the authors while starting high dose steroid. What etiology or condition did they have in mind at the time?

6. Along with the autoimmune thrombocytopenia and hepatitis referenced by the authors (refs 10,11) after COVID-19 vaccination, cases of the related condition rheumatoid arthritis after COVID-19 vaccination may also be mentioned as pathogenesis is broadly linked to Still's disease.

7. The authors discuss two main pathogenetic hypotheses. These may be split clearly in the written text for clarity (adenoviral vector induced and inflammatory cytokines induced). The direct toxicity of Spike protein or cross-reactive antibodies may be mentioned as alternative pathogenetic models. Currently, this is a bit mixed up.

8. Causality assessment file as per old version (not new version) WHO scale for adverse events following immunization must be provided as supplementary material and the causality classification done accordingly- Definite or Probable or Possible, etc.

9. Optional but would be good- If possible the authors should mention whether the patient received the second dose also, and the SARS-CoV-2 anti-Spike IgG level in serum. High levels may be linked to adverse events. Even if not done, I would advise authors to perform this on a follow-up visit for their own knowledge.

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.
Reviewer Expertise: Geriatric pharmacovigilance, Geriatric neuropsychiatry, COVID-19 (vaccines)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Aug 2022
Sudeep Adhikari, Pyuthan Hospital, Pyuthan, Nepal

Dear reviewer,
Thank you for your constructive comments that have certainly helped improved the manuscript.
Below are point by point responses to your comments.
1. Kindly update the case and death numbers in Nepal to March 2022 figures
   Answer- Case and death numbers have been updated.
2. English language editing is much needed to improve clarity, in the Abstract, Introduction and Case Presentation parts.
   Answer- Revised as per the suggestion.
3. Use the word hepatitis instead of transaminitis.
   Answer- Hepatitis has been used.
4. Use bone marrow cytology (or histopathological examination of bone marrow biopsy sample) whichever is suitable, instead of histopathological bone marrow examination.
   Answer- Bone marrow cytology has been used.
5. Please mention the consideration made by the authors while starting high dose steroid. What etiology or condition did they have in mind at the time?
   Answer- The diagnosis of AOSD as per the Yamaguchi criteria was considered prior to giving high dose steroids.
6. Along with the autoimmune thrombocytopenia and hepatitis referenced by the authors (refs 10,11) after COVID-19 vaccination, cases of the related condition rheumatoid arthritis after COVID-19 vaccination may also be mentioned as pathogenesis is broadly linked to Still’s disease.
   Answer- Another article describing the development of seropositive RA has been added in the reference 12.
7. The authors discuss two main pathogenetic hypotheses. These may be split clearly in the written text for clarity (adenoviral vector induced and inflammatory cytokines induced). The direct toxicity of Spike protein or cross-reactive antibodies may be mentioned as alternative pathogenetic models. Currently, this is a bit mixed up.
   Answer- Revised as per the suggestion.
8. Causality assessment file as per old version (not new version) WHO scale for adverse events following immunization must be provided as supplementary material and the causality classification done accordingly- Definite or Probable or Possible, etc.
   Answer- Causality assessment file has been added as supplementary material.
9. Optional but would be good- If possible the authors should mention whether the
patient received the second dose also, and the SARS-CoV-2 anti-Spike IgG level in serum. High levels may be linked to adverse events. Even if not done, I would advise authors to perform this on a follow-up visit for their own knowledge.

1. Answer- The patient did not receive the second dose of the vaccine. And the serum level of the anti-spike protein IgG was not performed as it was unavailable.

**Competing Interests:** No competing interests were disclosed.

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**Reviewer Report 31 January 2022**

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The authors describe a case of AOSD following COVID-19 vaccination. Though rheumatic disease flare is a known complication of vaccination, development of new disease is less common. AOSD has been reported earlier with COVID-19 as well as with vaccination. This case highlights that if you have persistent fever, leucocytosis thrombocytosis rash and arthritis and no infectious agent or autoantibodies are negative AOSD should be considered.

AOSD is a diagnosis of exclusion thus it should be emphasized that common diseases must be excluded before prescribing steroids.

**Is the background of the case's history and progression described in sufficient detail?**

Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

Yes

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**

Yes

**Is the case presented with sufficient detail to be useful for other practitioners?**

Yes
Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Rheumatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 10 Aug 2022

Sudeep Adhikari, Pyuthan Hospital, Pyuthan, Nepal

Dear Reviewer,
Thank you for your feedback to this manuscript.

Competing Interests: none