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Case Report

SARS-CoV2 vaccination-induced erythema nodosum: A case report

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Abstract Erythema nodosum (EN) is acute nodular septal panniculitis characterized by firm nodule or erythematous plaque which is pain on palpation and commonly localized on lower extremities. EN cases related to various vaccinations have been reported with the onset of <24 hours to 30 days of first or following dose. Some studies have reported EN case after COVID-19 vaccination in adult. We reported a case of 25 years old male presented with tender, erythematous nodules on the bilateral lower extremities that started one day after receiving second dose of COVID-19 vaccination. Based on patient history, physical examination, laboratory, and histopathologic investigation all pointed to EN related to vaccination. The patient was given nonsteroidal anti-inflammatory agent and clinical improvement was noticed.

Key words
COVID-19; Erythema nodosum; Vaccination.

Introduction

Vaccination of SARS-CoV-2 has been used worldwide over the past year as a mean of COVID-19 pandemic mitigation.[1] Although it has been shown to mostly being a safe and effective method, adverse effects, unfortunately, still occurs. There were several dermatologic reactions reported following COVID-19 vaccination, including erythema nodosum (EN). However, the pathogenesis and incidence are still unknown. It is hypothesized a type IV hypersensitivity/ delayed-type hypersensitivity reaction towards certain antigens contained in the vaccines.[2-4] We describe a case of EN occurring 24 hours following a second dose COVID-19 vaccination in an adult male patient.

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Case report

A 25-year-old male was consulted from the internal medicine department presented with multiple tender and erythematous nodules on his bilateral lower extremities. Pain exerts during heavy activity and patient notices darkening of the skin. Patient had no history of the same complaint. One day prior to presentation, the patient had just received his second dose of COVID-19 vaccine. He had no known recent history of fever, cough nor shortness of breath. Past medical history of tuberculosis, sarcoidosis, inflammatory bowel disease, and traumatic injury on lower extremities were denied by patient. Patient had not received therapy for this complaint.

On physical examination, the patient's vital signs were within normal limits. Dermatological

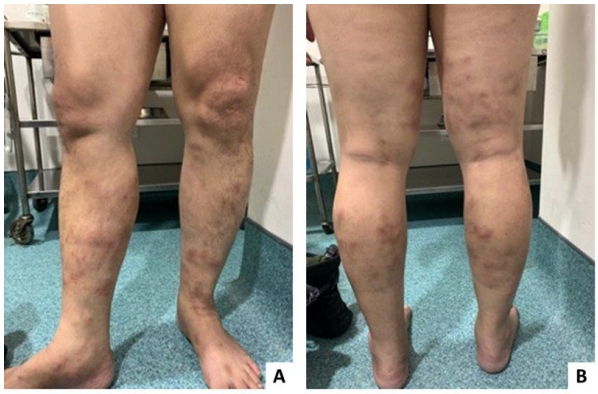

Figure 1 Erythematous nodules and macules along with hyperpigmented macules on both lower extremities.

examination revealed multiple tender erythematous and hyperpigmented nodules and macules were noted on bilateral lower extremities **(Figure 1)**. The lesions were slightly painful on palpation.

Laboratory testing of complete blood count, kidney function and liver function were within the normal ranges. Mantoux skin test was performed given the likelihood of *M. tuberculosis* infection and the result was negative. On chest X-Ray, no abnormalities were found. Histopathological examination using hematoxylin and eosin (H&E) staining taken from one of the nodules on the right lower extremity showed septal tissue thickening of subcutaneous tissue and typical Miescher radial granuloma, which is aggregation of small histiocytes around septal tissue **(Figure 2)**. The results suggested EN.

Based on findings of patient history, physical examination, laboratory, and histopathologic examination, the most likely diagnosis was EN. The patient received oral analgesics of natrium diclofenac 25mg twice daily and topical clobetasol cream applied twice daily, In addition, the patient was suggested to immobilize both legs and perform warm compression. Two weeks after receiving treatment, clinical improvements were evident with evolution to hyperpigmented nodules and the reduced pain. Four weeks after the first treatment, despite some hyperpigmented scars on the nodule sites, no new lesions were noticed.

Discussion

EN is an acute nodular septal panniculitis characterized by firm and painful nodule or erythematous plaque commonly localized on lower extremities.[5] The prevalence of EN is approximately 1-5 cases/ 100,000 individuals and are commonly seen between the ages of 18 and 34 years. The female to male ratio is 3-5:1.[6-9]

Approximately 50% of EN cases are idiopathic. Some known underlying causes of EN include infections, medications, sarcoidosis, pregnancy, inflammatory bowel disease, vaccination, autoimmune diseases, and paraneoplastic syndrome.[6] EN cases related to vaccinations have been reported within the first 24 hours-30 days of first or following doses.

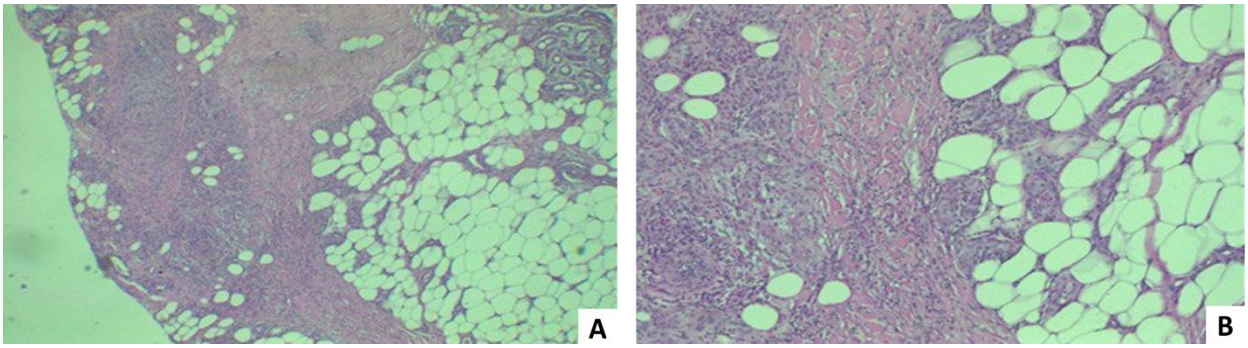

Figure 2 Septal tissue thickening of subcutaneous tissue and typical Miescher radial granuloma.

Regarding the SARS-CoV2 vaccination, some papers have reported EN cases after vaccination in adults in most types of vaccines. These include Medigen,[10] Moderna,[11] AstraZeneca,[4,12] Covishield,[13] and Pfizer-BioNTech.[14-16] Our patient developed EN 24 hours after the second dose of vaccination and was otherwise healthy.

Vaccines stimulate the innate immune response by triggering and increasing specific memory cells towards certain antigens. The most common adverse effects related to SARS-CoV2 vaccines vaccination include fever, headache, fatigue, and lymphadenopathy.[14] Furthermore, the most common cutaneous reactions post vaccination were mostly localized on the injection site. This includes erythema, edema, pain, induration, and pruritus within the first 7 days of injection. Pain usually resolves within 24-48 hours. Other more rare cutaneous reactions include urticaria, morbilliform eruptions, pernio, pityriasis rosea, erythromelalgia, erythema multiforme, and EN.[16,17]

The diagnosis of EN can be made clinically. However, in uncertain cases, histopathological examinations through biopsy can be performed. In addition, the identification of other possible underlying etiologies such as *Streptococcal* infection and tuberculosis, as well as diseases such as sarcoidosis is needed.[6,18] EN related to vaccination can be caused either due to reaction towards the antigens or adjuvant substances contained in the vaccine. Wu *et al*. reported a case of recurrent EN in a 37-year-old female patient one day after receiving second dose of Pfizer-BioNTech.[15]

Histopathological findings commonly reveal neutrophilic and lymphocytolytic infiltration from the interlobular septum of the subcutaneous adipose tissue (septal panniculitis). True vasculitis is not typically found. However, inflammation and hemorrhage can still be present in peripheral arteries. In early lesions, the dominant typical finding is septal edema, while in chronic lesion thickening of septum and fibrosis are present. Multinucleated giant cells and Miescher radial granuloma were also found in this case. Miescher radial granuloma suggests nodular aggregation of small histiocytes and macrophages arranged around a central star-shaped cleft, which is typically found in EN cases.[6]

EN is a self-limiting disease that usually resolve in several weeks. Treatment is not necessary especially in mild cases. Several symptomatic modifications and treatments that could help alleviate pain and inflammation include leg elevation, rest, and use of compression stocking. Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) is the first line treatment for EN. While in more severe cases, systemic corticosteroids (prednisone 20 mg/day for 7-10 days) can be given and is mostly effectively.[18] Our patient showed improvement after receiving oral natrium diclofenac and topical clobetasol within two weeks of treatment. However, scarring was also found within four weeks of onset.

Conclusion

EN is an acute panniculitis that can be caused by several underlying conditions. The association between SARS-CoV2 vaccines and EN, should be made after thorough history taking and physical examination to exclude other possible causes, along with a recent history of vaccination. It is imperative that physicians are aware of the possible cutaneous adverse events associated with SARS-CoV2 vaccines.

References

1. Padda IS, Parmar M. COVID (SARS-COV-2) Vaccine. StatPearls. 2021.

2. Niebel D, Wenzel J, Wilsmann-Theis D, Ziob J, Wilhelmi J, Braegelmann C. Single-Center Clinico-Pathological Case Study of 19 Patients with Cutaneous Adverse Reactions Following COVID-19 Vaccines. *Dermatopathology*. 2021;**8(4)**:463-76.
3. Herrera M, West K, Holstein H. Erythema Nodosum-Like Rash After Sars-Cov-2 Vaccination: A Case Report. *Chest*. 2021;**160(4)**:A1380.
4. Hali F, Marmech C, Chiheb S, Alatawna H. Erythema nodosum manifestation post COVID-19 vaccine: a case report. *World J Vaccines*. 2021;**11(3)**:33-8.
5. Hafsi W, Badri T. Erythema nodosum. StatPearls. 2021.
6. Leung AK, Leong K, Lam JM. Erythema nodosum. *World J Pediatr*. 2018;**14(6)**:548-54.
7. De Simone C, Caldarola G, Scaldaferri F, Petito V, Perino F, Arena V, et al. Clinical, histopathological, and immunological evaluation of a series of patients with erythema nodosum. *Int J Dermatol*. 2016;**55(5)**:e289-e94.
8. Chowaniec M, Starba A, Wiland P. Erythema nodosum–review of the literature. *Reumatologia*. 2016;**54(2)**:79.
9. Hafsi W, Badri T. Hirsutism. 2017.
10. Hsu H-T, Su H-A, Chen Y-C. Erythema nodosum, after Medigen vaccination against COVID-19? *J Formos Med Assoc*. 2022; **121(3)**:723–4.
11. Teymour S, Ahram A, Blackwell T, Bhate C, Cohen PJ, Whitworth JM. Erythema Nodosum after Moderna mRNA-1273 Covid-19 Vaccine. *Dermatol Ther*. 2022:e15302.
12. Cameli N, Silvestri M, Mariano M, Bennardo L, Nisticò SP, Cristaudo A, et al. Erythema nodosum following the first dose of ChAdOx1-S nCoV-19 vaccine. *J Eur Acad Dermato*. 2022;**36(3)**:e161-e2.
13. Mehta H, Handa S, Malhotra P, Patial M, Gupta S, Mukherjee A, et al. Erythema nodosum, zoster duplex and pityriasis rosea as possible cutaneous adverse effects of Oxford–AstraZeneca COVID-19 vaccine: report of three cases from India. *J Eur Acad Dermatol*. 2022;**36(1)**:e16-e8.
14. Aly MH, Alshehri AA, Mohammed A, Almalki AM, Ahmed WA, Almuflihi AM, et al. First Case of Erythema Nodosum Associated With Pfizer Vaccine. *Cureus*. 2021;**13(11)**:e19529.
15. Wu X, Lim JHL, Lee JSS, Chio MT-W. Recurrent erythema nodosum after the second dose of the Pfizer-BioNTech BNT162b2 COVID-19 messenger RNA vaccine. *JAAD Int*. 2022;**6**:107-8.
16. Damevska K, Simeonovski V. Covid-19 vaccine associated erythema nodosum: Factors to consider. *Dermatol Ther*. 2022:e15410.
17. Sun Q, Fathy R, McMahon DE, Freeman EE. COVID-19 vaccines and the skin: the landscape of cutaneous vaccine reactions worldwide. *Dermatol Clin*. 2021;**39(4)**:653-73.
18. Kroshinsky D, Callen J, Ofori A, Post TJU. Erythema nodosum. UpToDate Inc Waltham (MA); 2021.