Erythema Nodosum after the second dose of the Pfizer-BioNTech COVID-19 messenger RNA vaccine

İkinci doz Pfizer-BioNTech COVID-19 messenger RNA sonrası gelişen Eritema Nodozum olgusu

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Dear Editor,

Erythema nodosum (EN) is a panniculitis characterized by acute onset inflammation of the subcutaneous fat tissue. The etiology can be variable with the majority as idiopathic or associated with certain conditions such as infections (especially beta-hemolytic streptococcus, tuberculosis), medications (sulfa drugs), pregnancy, inflammatory bowel diseases, Behçet's syndrome, sarcoidosis, and malignancies [1]. EN is typically manifested with painful, tender, nodular, and erythematous lesions particularly involving pretibial surfaces bilaterally. The occurrence of EN after vaccination is rare with limited number of reports in the literature. Herein we describe a case of EN developed following Pfizer-BioNTech COVID-19 mRNA vaccine.

33-year-old non-obese man presented with symmetrically distributed extensive erythematous, painful, tender, nodular lesions on the anterior tibia. Eight days prior to admission, he was given the second dose of COVID-19 Pfizer-BioNTech mRNA vaccine. The patient reported that no adverse events were seen during implementation of first dose of the same vaccine 4 weeks apart. No evidence of a recent infection or medication use was described. His past medical history was otherwise unremarkable. Physical examination revealed multiple erythematous tender nodules on pretibial surfaces, which are painful on palpation, consistent with EN diagnosis (Fig. 1-2). Laboratory investigations showed normal blood cell count, renal and hepatic functions, elevated C-reactive protein (CRP) (41 mg/L (reference: < 5.0 mg/L)) and erythrocyte sedimentation rate (ESR) (45 mm/h (reference: < 20 mm/h)). Microbiologic examination and chest X-ray were also nonrevealing. Histopathologic evaluation demonstrated widened subcutaneous septae containing inflammatory infiltrations of lymphomononuclear cells, neutrophils, eosinophils, and histiocytes, consistent with EN. Treatment with ibuprofen led to complete resolution of the lesions within three weeks. No relapse was seen thereafter even after the implementation of second booster of Pfizer-BioNTech COVID-19 mRNA vaccine.

EN is considered a hypersensitivity response to a variety of antigenic stimuli. It has been proposed that EN may be the result of the formation of immune complexes and their deposition in the venules of the septae of the subcutaneous fat [2]. High levels of cytokines, several adhesion molecules, inflammatory mediators, and growth factors, mainly involved in neutrophil recruitment and activation, have been reported both in the skin and serum of patients with EN [3]. As new onset of EN after receiving vaccination is uncommon, the pathogenesis of this rare phenomenon is still an area of investigation. It may be linked to the antigen of the infectious disease or adjuvant components [4]. According to a previous study, EN can be seen following certain vaccines including Bacillus-Calmette-Guerin, hepatitis B, human papillomavirus, malaria, rabies, smallpox, tetanus, diphtheria, and pertussis, and typhoid and cholera [4].

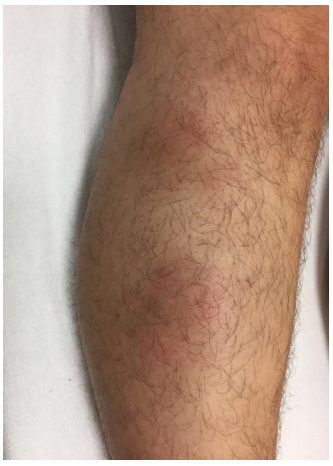

Fig. 1: Multiple erythematous nodules on right leg pretibial surfaces

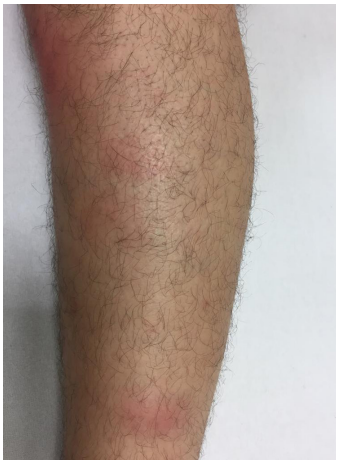

Fig. 2: Multiple erythematous nodules on left leg pretibial surfaces

Vaccines can elicit a strong CD4+ T cell immunologic response via triggering inflammatory cytokines including interferon gamma and alpha. Moreover, mRNA vaccines have also played an important role in humoral response comprised of IgG and IgM antibodies [5]. To date, seven cases of mRNA vaccine related EN have been published (with our case). Interestingly, EN was seen after the second in two cases and after the first dose in four cases. In one case, EN developed following the first and second doses [6,7,8,9]. The ''trained immunity'' is a recently described phenomenon that increased exposure to antigens such as an infection or a vaccine can potentiate the responsiveness of

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immune system elements with a repeated antigenic stimulus after a certain time, which in turn may cause autoimmune conditions. This can explain the reason of why adverse events are more common especially after the second dose. Indeed, mRNA vaccines have played undeniably a critical role in controlling the burden of COVID-19 pandemic and their efficacy has been well-identified. On the other hand, all clinicians should be aware that rare conditions such as EN, in our report, can be seen following implementation of these vaccines. However, as the causality is unclear, an extensive investigation of such a patient is still the cornerstone in diagnosis and management.

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