

## LETTER TO THE EDITOR

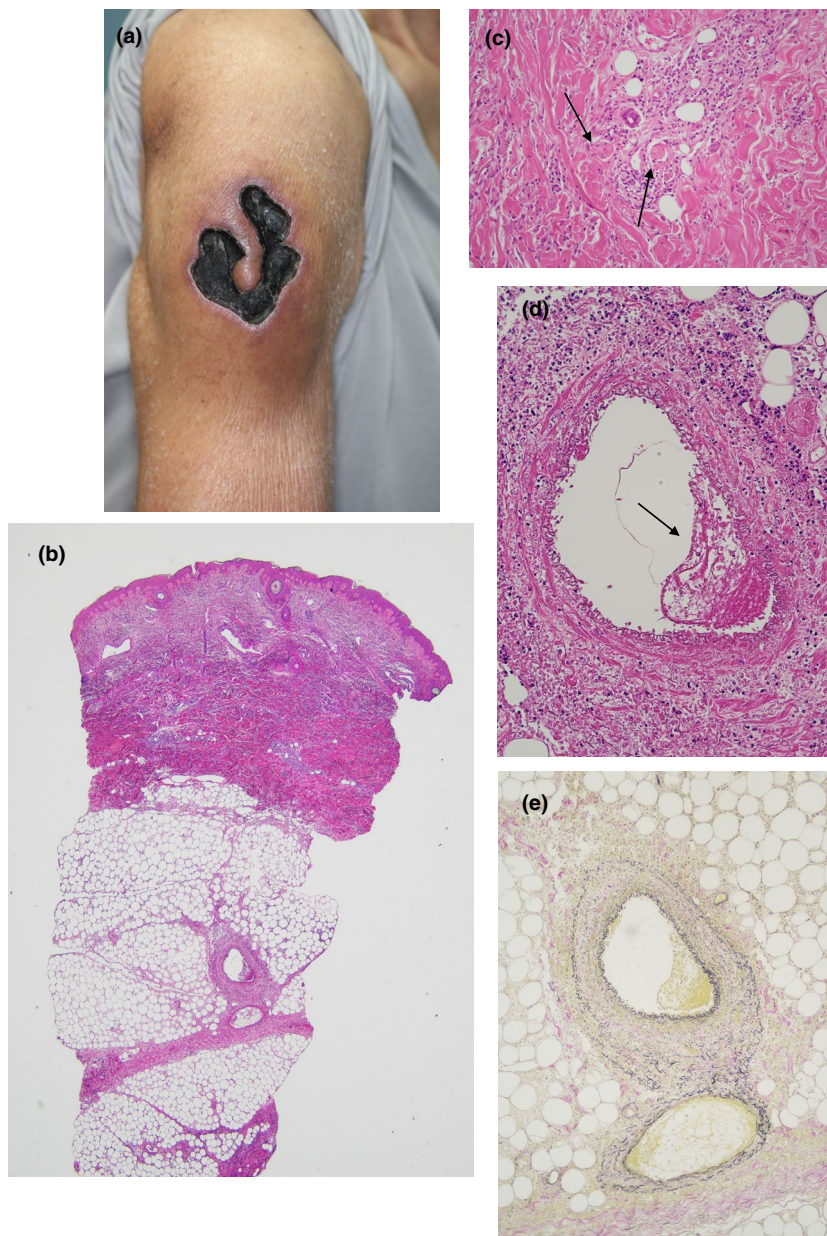
# Skin ulcer at the injection site of BNT162b2 mRNA COVID-19 vaccine

Dear Editor,

Since February 2021, coronavirus disease 2019 (COVID-19) vaccines have been administered to elderly persons aged over 65 years as a priority in Japan and reached nearly 100 million doses in 6 months. Meanwhile, a variety of adverse events have been reported including skin diseases such as a delayed hypersensitivity

reaction at the injection site (so called "COVID arm") as well as more systemic symptoms such as urticaria and disseminated erythematous rash.<sup>1</sup> Here, we report the first case to our knowledge of skin ulcer at the injection site.

A 79-year-old man was referred to us with a complaint of skin ulcer in the right upper arm, where the second dose of BNT162b2 mRNA



**FIGURE 1** (a) Clinical manifestation of the patient at first visit. (b) Whole view of the histopathology of biopsy from the erythema (hematoxylin–eosin [HE], original magnification  $\times 20$ ). (c) Perivascular lymphocytic infiltrate in the mid-dermis. Arrows indicate microthrombi (HE,  $\times 200$ ). (d) Degeneration of large vessel in the fat tissue with neutrophil infiltrates, nuclear dust, and red blood cell extravasation. Arrow indicates intravascular fibrin thrombus (HE,  $\times 200$ ). (e) Fragmentation of the internal elastic lamina of the affected muscular vessel (elastica van Gieson,  $\times 100$ )

vaccine had been administered a month prior. He experienced severe pain at the injection site on the second day and noticed an indurated erythematous nodule, in which an ulcer developed. At the visit, he had a large circinate, horseshoe-shaped necrotic ulcer with a diameter of 8 cm, surrounded by erythema (Figure 1a). Histopathological features of the erythema revealed an edema in the mid- to upper dermis, collagen proliferation in the deep dermis, perivascular lymphocyte infiltrates in the dermis, and neutrophil infiltrates around the large vessels in the subcutaneous fat tissues. (Figure 1b). There were microthrombi in the deep dermis (Figure 1c). The large vessels in the subcutaneous adipose tissue showed intravascular fibrin thrombi (Figure 1d) and degenerative change with fragmentation of the internal elastic lamina by elastica van Gieson staining (Figure 1e), surrounded by dense neutrophils, nuclear dusts, and extravasation of red blood cells (Figure 1d). These histopathological manifestations strongly suggested neutrophilic necrotizing vasculitis and thrombosis-mediated vessel destruction, which seemingly resulted in necrosis and consequent ulceration of the overlying skin. The necrotic tissues were surgically removed by debridement and topically treated with sulfadiazine silver cream, and skin graft was performed.


Skin ulcer at the injection site of COVID-19 mRNA vaccine has never reported in the literature. This condition was clearly different from the delayed-type local reaction known as COVID arm,<sup>1</sup> in that he experienced a painful erythematous lesion the next day, followed by development of an ulcer characterized by histological changes including thrombosis and vascular damage. However, it should be noted that he suffered from rheumatoid arthritis (RA), for which he was treated with iguratimod and salazosulfasalazine, and untreated polycythemia vera (PV). RA and PV are associated with complication of neutrophilic vasculitis and arterial/venous thrombosis, respectively.<sup>2,3</sup> More importantly, the spike protein of SARS-CoV-2, which is encoded by the mRNA vaccine, binds to angiotensin-converting enzyme 2, leading to pro-thrombosis condition via the "adverse" angiotensin converting enzyme-angiotensin II-angiotensin type I, receptor axis.<sup>4</sup> Recently, cutaneous microthrombi were found in our previous case, who experienced morbilliform rash after administration of BNT162b2 mRNA vaccine.<sup>5</sup> In conclusion, attention should be paid to cutaneous thrombosis and vasculitis in those who have preceding diseases when given the COVID-19 mRNA vaccines.

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This manuscript contains original unpublished work and is not being submitted for publication elsewhere.

## CONFLICT OF INTEREST

None declared.

Natsuko Aoki  
Yusuke Saruta  
Sae Tanaka  
Riho Nakajima  
Hozumi Sano  
Shigetoshi Sano 

Department of Dermatology, Kochi Medical School, Kochi University, Nankoku, Japan

## Correspondence

Shigetoshi Sano, Department of Dermatology, Kochi Medical School, Kochi University, Nankoku, Japan.  
Email: sano.derma@kochi-u.ac.jp

## ORCID

Shigetoshi Sano  <https://orcid.org/0000-0002-9812-0216>

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