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Cutaneous leukocytoclastic vasculitis following COVID-19 vaccination with Ad26.COV2.S vaccine: a case report and literature review

Laura Đorđević Betetto[1], Boštjan Luzar[2,3], Živa Pipan Tkalec[2], Svjetlana Ponorac[1,3] ✉

[1]Department of Dermatovenereology, University Medical Centre Ljubljana, Ljubljana, Slovenia. [2]Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia. [3]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

Abstract

Cutaneous vasculitis is a recognized and potentially serious adverse event of immunization with several vaccines, and COVID-19 vaccines are no exception. We present a case of cutaneous leukocytoclastic vasculitis occurring 17 days after inoculation with adenoviral vector vaccine (Ad26.COV2.S) in a previously healthy 30-year-old patient with no history of prior adverse events following vaccination. Transient laboratory abnormalities (mild proteinuria, cryoglobulinemia, and slightly diminished C3 complement level) were also noted, but they resolved with the resolution of skin changes after treatment with topical steroids. Although the frequency of cutaneous vasculitis after COVID-19 vaccines is extremely low, it presents an important challenge for the clinician when faced with an uncertain and delicate decision whether these patients can safely receive booster doses of COVID-19 vaccine. Because vaccination certificates are necessary for day-to-day activities and have a limited validity date, this may be an uncomfortable issue.

Keywords: cutaneous small vessel vasculitis, leukocytoclastic vasculitis, COVID-19 vaccine, Ad26.COV2.S, adverse events, cryoglobulinemia

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Introduction

The COVID-19 pandemic is one of the greatest challenges not only in modern medicine but even in modern history. The need to stop the high transmission rate and mortality led to the rapid development of various types of vaccines and their authorization for use. Because the number of immunized persons worldwide is increasing, reports of post-vaccination cutaneous adverse events have also begun to emerge. The incidence of cutaneous adverse events after COVID-19 vaccines is low, with local injection site reactions, delayed large local reactions, urticaria, and morbilliform eruptions most frequently reported (1, 2). Severe cutaneous adverse events are even more rare, with only a few cases reporting cutaneous vasculitis (1, 3–15).

We present a case of cutaneous leukocytoclastic vasculitis (CLV) occurring 17 days after inoculation with adenoviral vector vaccine (Ad26.COV2.S).

Case report

A 30-year-old previously healthy male patient presented to our dermatology department in October 2021 with a 10-day history of painful hemorrhagic papules and vesicles on his soles, shins, and elbows. He denied abdominal pain, hematuria, or gastrointestinal, musculoskeletal, or respiratory symptoms. Apart from receiving the first dose of COVID-19 adenoviral vector vaccine (Ad26.COV2.S) 17 days prior to the occurrence of the lesions, his medical history was unremarkable. He denied any signs of infection or taking new medications or dietary supplements. He also denied any previous drug- or vaccine-associated adverse events.

On clinical examination, purpuric and hemorrhagic nonblanching papules and vesicles, some with central erosions, were present on both soles and spreading onto the dorsum of the feet and distal part of the legs. Some hemorrhagic vesicles were also present on the elbows. The lesions on the soles were painful and more nodular on palpation (Fig. 1). There was no mucosal involvement or lymphadenopathy, and the rest of the clinical examination was normal.

Laboratory blood examinations (complete blood count, comprehensive metabolic panel, international normalized ratio, C-reactive protein, erythrocyte sedimentation rate, liver function panel, blood urea nitrogen, creatinine, and glomerular filtration rate) revealed mild leukocytosis (10.3; reference range 4.00–10.00 10^9/l), neutrophilia (8.24 and 80%; reference range 1.50–7.40 10^9/l and 40.0–80.0%), and a slightly elevated erythrocyte sedimentation rate (18; reference range 0–15 mm/h). Urinalysis showed moderate proteinuria (2), and the urine sediment examination showed borderline erythrocyturia (3; reference range up to 3). Further etiopathological laboratory workup (anti-neutrophil cytoplasmic antibodies, cryoglobulins, anti-nuclear antibodies, extractable nuclear antigen antibodies, anti-double stranded DNA antibodies, antiphospholipid antibodies, and rheumatoid factor) was negative.

A punch biopsy from the left foot was performed and showed erosion of the epidermis and papillary dermis with surrounding reactive changes and only discrete vasculitis changes, suggestive of secondary vasculitis. For direct immunofluorescence (DIF) microscopy, a skin sample was frozen in liquid nitrogen and cryostat sections were stained with FITC-labeled antisera to human immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), complement component 3 (C3), complement component 1q (C1q), and fibrin/fibrinogen (DakoCytomation, Denmark). The results were positive for granular deposits of IgM, C3, and fibrin/fibrinogen in the walls of the small vessels in the dermis, potentially compatible with vasculitis, although this could also be unspecific or secondary (Fig. 2).

✉ Corresponding author: svjetlana.ponorac@kclj.si

The patient was instructed to rest and was prescribed a potent topical corticosteroid cream. At a checkup 10 days later, we observed some new lesions on the feet and regression of the lesions on the elbows. A punch biopsy from a lesion on the foot was repeated, and the histopathology changes were now more evident and consistent with leukocytoclastic vasculitis (Fig. 3). The results of DIF were similar to the previous examination and showed granular deposits of IgM, C3, and fibrin/fibrinogen in the walls of the small vessels in the dermis (Fig. 2). A diagnosis of cutaneous small vessel vasculitis (SVV) was established; the patient was admitted, and further diagnostic evaluation proceeded.

Chest X-ray and abdominal ultrasound were normal. Routine laboratory tests and additional specific blood tests (serum protein electrophoresis, fibrinogen, D-dimer, lactate dehydrogenase, lupus anticoagulants, cold agglutinins, complement activation assay, and levels of C3 and C4 complement) revealed a slightly lower level of complement C3 (0.55; reference range 0.60–1.30 g/l) and C4 level at the lower limit (0.10; reference range 0.10–0.30 g/l), but these were otherwise within normal limits. Cryoglobulins were incidentally re-ordered and were surprisingly positive (the titer was not determined). Serologies for Epstein–Barr virus, human immunodeficiency virus (HIV), syphilis, hepatitis B virus (HBV), and hepatitis C virus (HCV) were negative, as well as SARS-CoV-2 RT-PCR of the nasopharynx. Repeated fecal occult blood test and urinalysis were normal. Due to previously detected proteinuria, a nephrologist was consulted, who excluded renal involvement.

Because a steady regression of skin lesions was noted, we continued treatment with local corticosteroids, which resulted in somewhat slow but complete regression of skin lesions after a few weeks. At a checkup, a laboratory test for cryoglobulins was repeated and was negative. With regard to no other instigating event, negative diagnostic evaluation of commonly recognized causes of vasculitis, and a clear temporal association, our patient's cutaneous vasculitis was linked to the Ad26.COV2.S vaccine. The patient was referred to an allergologist for evaluation regarding whether he can receive other COVID-19 vaccines in the future. A report of an adverse event was also submitted to the national drug and vaccine adverse event reporting system.

Discussion

CLV is a SVV (16) in which a predominant neutrophil inflammation and leukocytoclasia surrounding cutaneous vessels can be seen on histopathology (17, 18). Leukocytoclasia is a process in which neutrophils undergo death and break down, releasing nuclear debris, also called nuclear dust (17). The terms *cutaneous SVV* and *CLV* are often used interchangeably because most cases of cutaneous SVV show leukocytoclasia on histopathology (19,

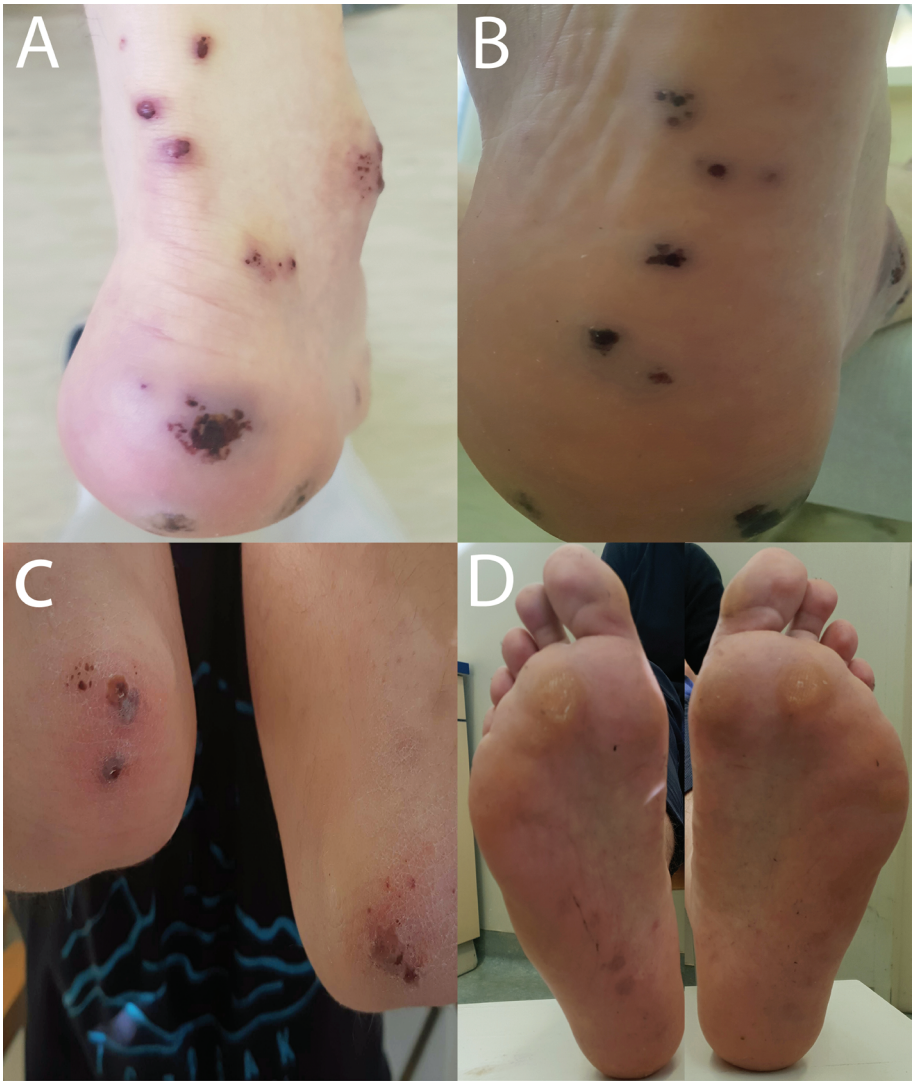

Figure 1 | Clinical presentation, patient at the time of presentation: palpable purpuric non-blanching deeply set tender papules and vesicles, some with central erosions on the A) ankle, B) sole, and C) elbows; patient at last control examination: D) complete regression of skin changes with only a few discrete hyperpigmented macules on the soles.

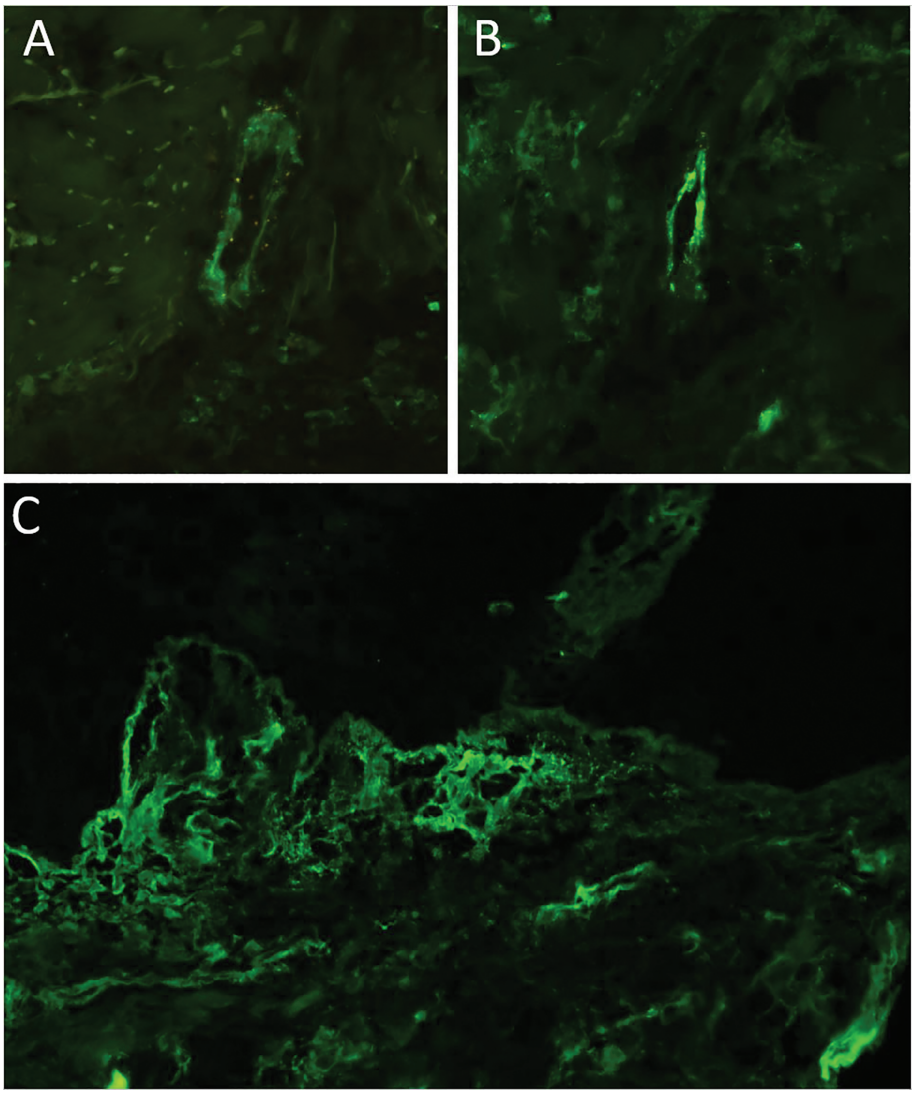

Figure 2 | Direct immunofluorescence revealed A) IgM, B) C3, and C) fibrinogen deposits in the dermal vessel walls (magnification: 400× in A and B, 200× in C). IgM = immunoglobulin M, C3 = complement component 3.

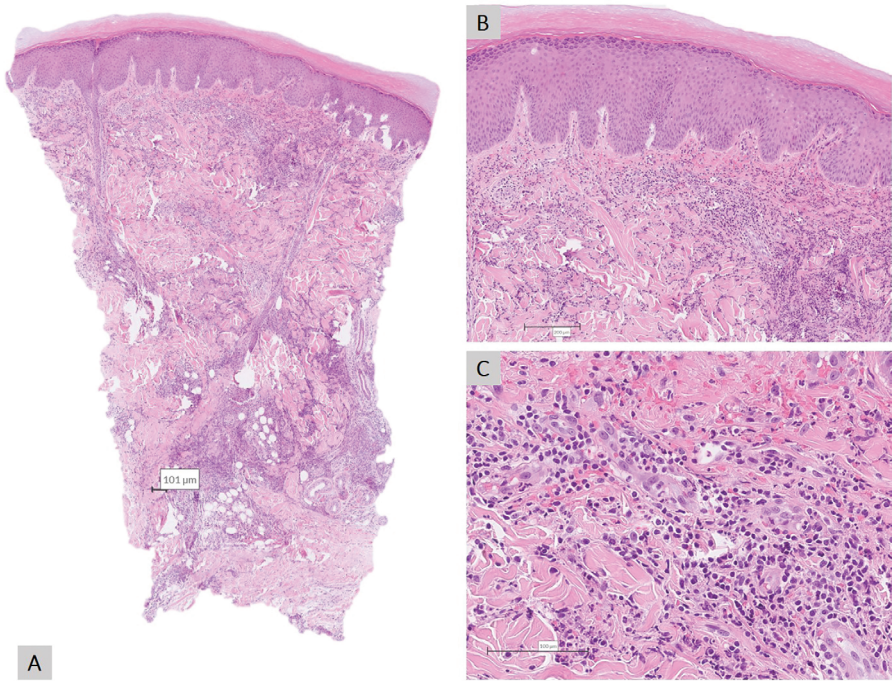

Figure 3 | Histopathologic changes characteristic of leukocytoclastic vasculitis: A) low-power magnification showing acral skin with dense superficial and deep perivascular and interstitial inflammatory cell infiltrate accompanied by extravasation of erythrocytes; B) intermediate-power magnification revealing perivascular and interstitial inflammatory cell infiltrate with extravasation of erythrocytes; C) high-power magnification; endothelial cells of the superficial vascular plexus are swollen. Note also extravasation of erythrocytes, perivascular and interstitial mixed inflammatory cell infiltrate, and nuclear debris.

20). CLV is most often idiopathic, but it can be triggered by infections, medications, underlying systemic diseases, or vaccinations (21). Different types of cutaneous vasculitis have been reported after vaccines, most often secondary to influenza vaccine. Nevertheless, vasculitis appears to be a very rare post-vaccination adverse event, and its exact pathogenesis remains unclear (22).

Cutaneous vasculitis secondary to COVID-19 vaccines is extremely rare, but it has been reported (1, 3–15), most often after messenger RNA (mRNA)–based vaccines. It includes new-onset vasculitis or aggravation of preexisting vasculitis (6, 12, 15). A recent study of 414 cases of cutaneous adverse events after mRNA COVID-19 vaccines reported frequencies of vasculitis of 2.9% (BNT162b2) and 0.7% (mRNA-1273) (1). To date, only six cases of CLV have been reported after the application of adenoviral vaccines: five after ChAdOx1 nCoV-19 (3, 5, 9) and one after the Ad26.COV2.S vaccine (7).

Cutaneous vasculitis can also be one of the complications of COVID-19 infection (23–26). A recent systematic review of the published literature on COVID-19–associated vasculitis found only nine published cases of various types of vasculitis (27). This incidence is probably underestimated, especially with regard to the possible spontaneous regression of cutaneous vasculitis, limited healthcare access of patients during the pandemic, and restraint from non-urgent procedures, such as skin biopsy. Interestingly enough, there seem to be more reported cases of vasculitis after COVID-19 vaccine than after natural infection. Whether this is because their incidence is truly higher or merely the consequence of vigilant attentiveness after new vaccine implementation remains to be determined. Cutaneous vasculitis after COVID-19 infection could be linked to aberrant activation of the immune system due to cross-reactivity and molecular mimicry of the viral antigens with self-antigens (28). Because some of the vaccine proteins are analogous to viral antigens, the pathogenetic mechanism may be the same in cutaneous vasculitis after COVID-19 vaccination. Vaccine antigens may thus cause a pro-inflammatory cascade, resulting in antibody formation and successive immune complex deposition in small vessels (13).

In our case, CLV was also accompanied by transient laboratory abnormalities, such as mild proteinuria, low complement levels, and cryoglobulinemia. This constellation of laboratory changes and CLV has been reported in two other patients after COVID-19 vaccination (11, 15) and also after pneumococcal (29) and influenza (30) vaccinations. In our patient, cryoglobulins were negative at the time of first presentation, and cryoglobulinemia occurred more than a month after initial cutaneous symptoms. This peculiarity points toward a clinically insignificant transient cryoglobulinemia, unlike two other cases, in which true cryoglobulinemic vasculitis developed (15, 29). Detectable cryoglobulins, without clinical manifestations of vasculitis, can be found even in healthy individuals, but they are particularly common in patients with connective tissue disorders, such as systemic lupus erythematosus (31), and chronic infections such as HIV and HCV, and especially HIV and HCV coinfections (32–34). The transient nature of these laboratory changes combined with the onset of vasculitis in a previously healthy individual only heightens the probability of an immune-mediated etiopathological link with the COVID-19 vaccine. Although we cannot exclude the coincidental onset of vasculitis, the temporal association with COVID-19 immunization and no other instigating event support their causal relationship.

Finally, because the COVID-19 certificate of our patient is about to expire, we are faced with another delicate decision: can patients that have experienced cutaneous vasculitis or other potentially serious cutaneous adverse events after COVID-19 immunization receive a booster dose and, if so, which type of vaccine is safe for them to receive? A study on cutaneous adverse events following mRNA COVID-19 vaccines reported that cutaneous reactions to mRNA COVID-19 vaccines are generally mild and transient. Fewer than half (43%) of the patients that experienced cutaneous adverse events following the first dose experienced the same after the second dose. It was therefore concluded that cutaneous adverse events are not a contraindication for further doses (1). However, in cases of cutaneous vasculitis or other potentially serious adverse events, the answer is more complex and uncertain.

Nevertheless, the substantial repercussions of the COVID-19 pandemic on physical and psychological health, as well as on socioeconomic aspects of life, underscore the need for increasing the global immunization rate and getting the virus under control.

Conclusions

Cutaneous vasculitis is a recognized and potentially serious adverse event of immunization with several vaccines, and COVID-19 vaccines are no exception. Its frequency seems to be extremely rare, although that might increase with immunization coverage rates. Because vaccination certificates are becoming necessary for day-to-day activities but have a limited validity date, doctors may be faced with the delicate decision of determining whether booster doses of COVID-19 vaccines are safe for such patients.

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