Cutaneous small vessel vasculitis associated with palpable purpura after COVID 19 Vaccination: A case report and a literature review

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Abstract

Coronavirus disease 19 (Covid-19) vaccination is mostly safe and effective: adverse events following Covid-19 vaccination are generally mild and well tolerated. Adverse reactions may include cutaneous reactions and, rarely, cutaneous small vessel vasculitis associated with palpable purpura. We present the case of a small-vessel vasculitis after Covid-19 vaccination that manifested with no organ involvement or systemic symptoms, associated with self-resolution, and a review of the cases described in literature. We have collected the epidemiological and clinical features of these cases.

Keywords: Small vessel vasculitis; Covid-19 vaccination; Adverse reaction; Cutaneous reaction.

1. Introduction

Several adverse reactions of Coronavirus disease 2019 (Covid-19) vaccines have been reported, although vaccination is generally safe.

Among possible adverse events, multiple skin reactions has occasionally been reported: the most frequently is unspecific injection-site reaction, but also inflammatory reactions in dermal filler, morbilliform and erythema multiforme-like rashes (1-4), type I hypersensitivity reactions (urticaria, angio-oedema, anaphylaxis), type IV hypersensitivity ("COVID arm" ), functional angiopathies (erythromelalgia), pityriasis rosea-like rashes and reactivation of herpes zoster.

Lastly, other immune-mediated skin reactions (such as leukocytoclastic vasculitis) have been reported after Covid-19 vaccination [1]. We reported a case of a palpable purpura associated with vasculitis after Covid-19 vaccination without organ involvement or systemic symptoms, associated with self-resolution.

In the end, we performed a systematic review of the cases described in literature and we collected the epidemiological and clinical features of these cases. In particular, we analyzed epidemiological features, type of vaccination, symptoms, laboratory texts, comorbidity, trigger, clinical latency, site of reaction, outcome, histology, both in our case and in literature cases.

The course of most cases is moderate and complete remission could be achieved in numerous patients [1,2]. Furthermore, small vessel vasculitis after Covid-19 vaccination does not necessarily have a causal relationship, but it is important to know possible adverse events to help improve patient safety.
2. Material and methods

We present the case of small vessel vasculitis associated with palpable purpura after Covid-19 vaccination and a systematic review of cases published in the literature.

We did accurate research on PubMed, investigating cases of small vessel vasculitis after Covid-19 vaccination (Keywords "Covid-19 vaccination" AND "cutaneous vasculitis", with detailed control of references).

We have extended our search by using other web search engines with the same keywords (Google).

Cases of cutaneous vasculitis after Covid-19 vaccination were determined on the basis of the following criteria:

- Vasculitis in healthy individuals with no active manifestations related to autoimmunity.
- Cutaneous vasculitis limited to the skin without visceral involvement.
- Temporal relationship between the Covid-19 vaccination (any vaccine) and the development of clinical manifestations.

We reported 29 cases [5-30], we excluded some articles for age limit (adult: 19+ years), language limit (English language), reporting a total of 24 cases (Table1).

Table 1 Epidemiological and clinical characteristics of patients described in the literature
Table 1 Epidemiological and clinical characteristics of patients described in the literature

<table>
<thead>
<tr>
<th>Case and reference</th>
<th>Type of vaccination</th>
<th>Year</th>
<th>Sex</th>
<th>Others symptoms</th>
<th>Lab text</th>
<th>Comorbidity</th>
<th>Other triggers</th>
<th>Clinical latency</th>
<th>Site</th>
<th>Outcome</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pfizer</td>
<td>84 year</td>
<td>Womán, caucasian</td>
<td>None</td>
<td>Slight alteration of TS, non-biological inflammation syndrome, aspecific ANA, 1/70</td>
<td>hypertensión</td>
<td>Influenza vaccination, small airways flogosis</td>
<td>20 days following the second vaccine dose</td>
<td>Lower limbs</td>
<td>Spontaneous resolution after 2 weeks</td>
<td>Not performed</td>
</tr>
<tr>
<td>2-4 (5)</td>
<td>Vaxzevria</td>
<td>57 year</td>
<td>man, Caucasian</td>
<td>None</td>
<td>Non-specific increases in VES, CRP</td>
<td>Hypertensión</td>
<td>None</td>
<td>14 days following the first vaccine dose</td>
<td>Lower limbs and rapidly spreading to the abdomen, torso, and head</td>
<td>Resolution over 3 weeks with 1 mg/kg PD</td>
<td>Not performed</td>
</tr>
<tr>
<td></td>
<td>Vaxzevria</td>
<td>58-year</td>
<td>Man, Caucasian</td>
<td>None</td>
<td>Non-specific increases in VES and CRP</td>
<td>None</td>
<td>None</td>
<td>7 days following the second dose of vaccine</td>
<td>Lower limbs, abdomen and trunk</td>
<td>0·5 mg/kg PD, with no clinical benefit, then 1 mg/kg PD, with progressive resolution of skin lesions over 10 day</td>
<td>Not performed</td>
</tr>
<tr>
<td></td>
<td>Vaxzevria</td>
<td>53-year</td>
<td>Womán, Caucasian</td>
<td>None</td>
<td>Non-specific increases in VES and CRP</td>
<td>None</td>
<td>None</td>
<td>6 days following the first dose</td>
<td>Lower and upper limbs</td>
<td>1 mg/kg PD, which progressive resolution of skin lesions over 2 weeks</td>
<td>Mild lymphocytic perivascular infiltrate</td>
</tr>
<tr>
<td>5 (6)</td>
<td>Vaxzevria</td>
<td>71-year</td>
<td>Woman, Caucasian</td>
<td>None</td>
<td>11,880 white blood cells/mm3, D-dimer level 806 ng/ml, CRP 5.07 mg/dL, ANA, ENA, ANCA</td>
<td>History of fibrocystic mastopath y and arterial hypertensión on treated</td>
<td>Second dose of Vaxzevria COVID-19 vaccine (AstraZeneca) five days earlier</td>
<td>Skin lesions associated with burning sensation that appeared one day earlier on both legs</td>
<td>PD 20 mg daily, tapered over 14 days, with complete clinical resolution of the skin lesions.</td>
<td>LCV</td>
<td></td>
</tr>
</tbody>
</table>
negative, C3 and C4 levels respectively 83 mg/dL and <8 mg/dL. RF 17 U/L/mL.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Vaccine</th>
<th>First Dose</th>
<th>Sex</th>
<th>Race</th>
<th>Comorbidities</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7 (7)</td>
<td>Pfeizer</td>
<td>60 years</td>
<td>Woman</td>
<td>White British</td>
<td>None</td>
<td>Urine microscopy showed red cells 2 x 10⁶/L</td>
<td>Hypotiroidism</td>
<td>None</td>
</tr>
<tr>
<td>75 years</td>
<td>Pfeizer</td>
<td>None</td>
<td>None</td>
<td>White British</td>
<td>None</td>
<td>Hypertension</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>8-9 (8)</td>
<td>Vaxzevria</td>
<td>55 years old</td>
<td>Female, Caucasian</td>
<td>Fever, myalgia, left wrist swelling</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>48 years old</td>
<td>Vaxzevria</td>
<td>Male, Caucasian</td>
<td>Fever, myalgia</td>
<td>None</td>
<td>Hypertension</td>
<td>None</td>
<td>2 days after second dose, 7 days after the first dose of vaccine that resolved within 7 days</td>
<td>Over hands, forearms, gluteal region, and lower limbs similar lesions limited to ankles</td>
</tr>
<tr>
<td>10-12 (9)</td>
<td>Vaxzevria</td>
<td>57 years old</td>
<td>Man</td>
<td>None</td>
<td>Non-specific increases in VES and CRP</td>
<td>Hypertension</td>
<td>None</td>
<td>14 days following the first vaccine dose</td>
</tr>
<tr>
<td>Vaxzevria</td>
<td>Age</td>
<td>Gender</td>
<td>Symptoms</td>
<td>Tests</td>
<td>Dose</td>
<td>Treatment</td>
<td>Outcome</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>58-year-old man</td>
<td>Non-specific increases in VES and CRP</td>
<td>None</td>
<td>7 days following the second dose of vaccine</td>
<td>Spreading from the lower limbs to the abdomen and trunk</td>
<td>0-5 mg/kg PD, to no clinical benefit, and then 1 mg/kg PD, with progressive resolution of skin lesions over 10 days.</td>
<td>Not performed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53-year-old woman</td>
<td>Non-specific increases in VES and CRP</td>
<td>None</td>
<td>Purpura developed 6 days following the first dose</td>
<td>Lower and upper limbs.</td>
<td>PD 1 mg/kg, which led to a progressive resolution of skin lesions over 2 weeks</td>
<td>Mild lymphocytic perivascular infiltrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42-year-old woman, White</td>
<td>IgG and thyroid-stimulating hormone were slightly elevated</td>
<td>Hypertension and severe obesity</td>
<td>4 days after vaccination, first dose</td>
<td>Lower limbs up to the gluteal area</td>
<td>PD 30 mg/day, increased to 60 mg/day due to poor response. With this treatment the rash resolved over the next 5 days</td>
<td>LCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-year-old African American man</td>
<td>CRP 86 mg/L and VES 34 mm/hr, serum IgG, 3310 mg/dL.</td>
<td>Hypertension, hyperlipidemia, and mechanical aortic valve replacement (on warfarin)</td>
<td>None</td>
<td>7 days prior</td>
<td>Petechiae on the lower portion of the abdomen and palpable purpura on the left arm</td>
<td>Improved over the course of 4 days after initiation of oral and topical corticosteroids (PD 60 mg)</td>
<td>LCV</td>
<td></td>
</tr>
<tr>
<td>68-year-old Korean woman</td>
<td>Decreased C3 and C4 levels (68.3 and 2.4 mg/dL)</td>
<td>None</td>
<td>Both lower extremities</td>
<td>1 week, followed by 2 mg/day for 2 weeks), colchicine 1.2 mg/day, and topical methylprednisolone</td>
<td>LCV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The lesions resolved and did not relapse after cessation of treatment. The lesion slightly recurred on the legs with the second vaccination, but resolved spontaneously in a few days.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>COVA XIN (India)</th>
<th>31-year-old woman, Caucasian</th>
<th>None</th>
<th>None</th>
<th>Second dose of inactivated viral vaccine, 4 days prior to development of the lesion.</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>13</td>
<td></td>
<td></td>
<td>None</td>
<td>None</td>
<td>Purpura on the left leg, Rest and leg elevation, and antihistaminics for a week, after which the lesions resolved with hyperpigmentation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abundant upper and mid-dermal perivascular infiltrate.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Vaxzevria</th>
<th>77-year-old woman, Caucasian</th>
<th>None</th>
<th>Slight elevation of VES, CRP</th>
<th>None</th>
<th>None</th>
<th>First dose, latency no specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>14</td>
<td></td>
<td></td>
<td>None</td>
<td>PD 50mg per day started, tapered by 5 mg every three days. Additionally, dapsone 50 mg daily. Vasculitis resolved, but limited residual blanching macules and patches were still present on the previously affected sites. Recommended a different vaccine for the second dose.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCV 19 (16)</td>
<td>Pfizer-BioNTech</td>
<td>83-year-old</td>
<td>Caucasian woman</td>
<td>None</td>
<td>Elevated levels of CRP, VES, RF with hypocomplementemia and detection of cryoglobulin.</td>
<td>None</td>
<td>Approximately 5 days after her second dose</td>
<td>Bilateral palpable purpuric lesions with erythema and edema of her lower extremities</td>
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</tr>
<tr>
<td>20 (17)</td>
<td>Inactivated COVI D-19 vaccine</td>
<td>33-year-old</td>
<td>Caucasian man</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Three days after the first dose</td>
<td>Erythematous macules and palpable papules on the legs, forearms, and right belly, Five days later; Topical mometasone furoate was prescribed twice daily with partial resolution.</td>
</tr>
<tr>
<td>Case</td>
<td>Vaccine</td>
<td>Age</td>
<td>Sex</td>
<td>Race</td>
<td>Past Medical History</td>
<td>Symptoms</td>
<td>Duration</td>
<td>Treatment</td>
</tr>
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</tr>
<tr>
<td>21 (18)</td>
<td>Pfizer-BioNTech</td>
<td>46-year-old</td>
<td>Female</td>
<td>Caucasian</td>
<td>None</td>
<td>Past medical history of psoriasis, psoriatic arthritis, irritable bowel syndrome, and leukocytoclastic vasculitis</td>
<td>None</td>
<td>2 days</td>
</tr>
<tr>
<td>22 (19)</td>
<td>Vaxzevria</td>
<td>62-year-old</td>
<td>Female</td>
<td>Asian</td>
<td>None</td>
<td>Headache, myalgia, and symmetric large joint arthralgias</td>
<td>CRP 31 mg/L (&lt;5), low-titre ANA (1:80 speckled), raised FR (169 IU/mL [&lt;20]), depressed C4 complement</td>
<td>None</td>
</tr>
<tr>
<td>23 (20)</td>
<td>Pfizer-BioNTech</td>
<td>65-year-old</td>
<td>Male</td>
<td>Not reported</td>
<td>None</td>
<td>Diabetes and hypertension for which he is on metformin and lisinopril</td>
<td>None</td>
<td>2 days after receiving his third dose (booster)</td>
</tr>
<tr>
<td>Case</td>
<td>Vaccine</td>
<td>Age</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Timeline</td>
<td>Findings</td>
<td>Recovery</td>
<td>Notes</td>
</tr>
<tr>
<td>------</td>
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<td>-------</td>
</tr>
<tr>
<td>24</td>
<td>Moderna or Pfizer, not specified</td>
<td>23</td>
<td>Male</td>
<td>Not reported</td>
<td>Not reported</td>
<td>12 days after receiving the COVID-19 vaccine</td>
<td>Petechial macules on hands and pink blanching macules and papule on arms, chest, and legs</td>
<td>Recovery</td>
</tr>
</tbody>
</table>

3. Results

3.1. Case report

A caucasian 84-year-old woman came to our attention for the onset of petechiae and purpura in the lower limbs (Fig 1), in absence of other systemic symptoms (in particular no fever, arthomyalgia, pharyngodynia). Twenty days earlier she had vaccinated anticovid-19 (II dose). A day later the onset of symptoms she received influenza vaccination by the general practitioner. Subsequently, pain of the lower limbs associated to edema and extension of purpura appeared, for which she assumed 5 days later prophylactic heparin, because as raccomended by her family doctor. She also performed a chest x-ray, positive for thickening in the left base. Subsequently she was hospitalized.

Anamnesis showed only: no personal or family history of autoimmunity, no smoking , no drug allergies, the patient lived alone, autonomous, she had hypertension ( in therapy with nebivolol ½ cp), she reported epileptic seizures (during her youth, up to the menopause).

**Figure 1** Petechiae and purpura in the lower limbs of the our patient

Physical examination showed purpura extended to the lower limbs (see photos 1)

Laboratory tests revealed: normocytic anemia, slight alteration of transaminases (ALT 64 U / l), non-biological inflammation syndrome (WBC7670/mmc, Hb 10.7 g/dl, PLT 362000/mmc, CRP 7.8 mg/l). Coagulation parameters were normal.

HR chest CT, performed for pulmonary thickening, in the absence of biological inflammation syndrome showed ground glass opacity and tree-inbud aspects in the posterior segment of the right upper lobe, associated to mucous material in the lumen of the bronchial branches, as from small airways comonitant inflammation.

We hypothesized:

- An autoimmune etiology: in this regard systemic autoimmunity was negative: anti-neutropol cytoplasmatic antibody ( C-ANCA, P-ANCA), cryoglobulins, rheumatoid factor, anti DNA (only mild and nonspecific positivity, homogeneous pattern of ANA, 1/80).
- In the infectious hypothesis, the serology for Hepatitis B virus (HBV) and hepatitis C virus (HCV) , cytomegalovirus, Epstein-Barr virus, coxsackievirus, and human immunodeficiency virus (HIV) was negative.
- Study regarding organ involvement shows a negative electromyography (EMG) of the lower limbs. Proteinuria, complement, hepatorenal function and electrophoresis are also within the limits.

During hospital stay, the skin lesions gradually improved in one week, with total resolution after two weeks. An antibiotic course with azithromycin was performed due to bronchial flogosis. After one week, the patient was asymptomatic.

Purpuric rash on the legs raised the possibility of cutaneous small vessel vasculitis, although not confirmed by skin biopsy.
Indeed the skin biopsy is not performed as the rash had fully resolved by the time the patient first presented to the dermatology team. The appearance was however highly suggestive for small vessels vasculitis.

Therefore, after dermatological evaluation, only one course of topical therapy with diprosone was performed. Due to temporal proximity with the ante Covid-19 vaccination, we concluded for a small vessel vasculitis, triggered by anti Covid-19 vaccine. We interpreted influenza vaccination as intercurrent inciting events.

4. Discussion

Covid-19 vaccination are mostly safe and effective: adverse events to vaccinations are usually mild and well tolerated and may include cutaneous reactions [1-3]. From our case series, small vessel cutaneous vasculitis, not associated with organ localization, as in the case presented, is an unusual event, but described in the literature. Relationship between immunizations and vasculitis has to be determined. Cutaneous vasculitis after vaccination is reported most frequently after vaccine against influenza, hepatitis A and hepatitis B, Bacillus Calmette-Guerin (BCG), anthrax, Human Papilloma Virus (HPV), measles-mumps-rubella (MMR) and pneumococci, described as triggers for vasculitis, particularly cutaneous vasculitis [20,21].

Although in our patient’s purpura occurred in the absence of both thrombocytopenia and clinically apparent thrombosis an immune stimulation secondary to vaccine administration could be hypothesized (similar to vaccine-induced thrombotic thrombocytopenia). In our series, purpuric cutaneous vasculitis secondary to inactivated vaccines, as Vaxzevria COVID-19 vaccination is more frequent, but cutaneous vasculitis is also reported following mRNA vaccines (Pfizer more prevalent : 6/23 cases). In this regard, in a study with large number of cases (2 vasculitis following Moderna vaccination is described, but only urticarial vasculitis) [22-24].

To date, the exact mechanism of vaccine-associated cutaneous adverse reactions is unclear. It is supposed that autoreactive lymphocytes and cross-reactive antibodies due to molecular mimicry can cause autoimmune reactions, as in the case of immune thrombocytopenia (VT), lupus erythematosus and bullous pemphigoid after vaccination [2]. Probably RNA vaccines and inactivated vaccines share a similar adverse drug reaction profile.

It is known that that molecular mimicry exists between Covid-19 and human components (e.g. the spike-protein sequences used to design the vaccines), but the question is if skin complications after COVID-19 vaccination is true or related to causality.

Our review, with the limitations of the small number of cases, seems to show:

- From an epidemiological perspective, a vasculitis of small vessel after Covid-19 vaccination associated to purpuric manifestation without other organ involvement, has an average age of onset of 57.2 years (range 23-84 years), female sex is slightly prevalent (65% of cases).
- Rarely, in the absence of organ involvement, post-vaccine cutaneous small-vessel vasculitis is associated with systemic symptoms (13% of cases).
- Patients often do not have comorbidities and, among comorbidities, hypertension is not uncommon (41.6% of cases). The association, however, could be linked to the confounding bias of the high prevalence of hypertension in the general population (the prevalence of hypertension in general population ranged from 13% to 41%) [31].
- Intercurrent inciting events are never described, except in our clinical case, in which the influenza vaccination could have triggered the petechiae (this could only due to a temporal bias or a molecular mimicry mechanism?). Indeed in a retrospective cohort study, compared with administration of COVID-19 mRNA booster vaccines alone, simultaneous administration of COVID-19 mRNA booster and seasonal influenza vaccines was associated with significant increases in reports of systemic reactions during days 0 to 7 following vaccination [32]. However, in this study, vaccines were co-administered and adverse reactions were moderate and systemic. Other studies should be designed to evaluate the association between double, even deferred, vaccination and autoimmune reactions.
- From the laboratory point of view, a modest biological inflammation syndrome may be present (52% of cases), while very rarely a positive autoimmune serology or a complement consumption are observed.
- From a clinical point of view, the average latency of presentation is 6.7 days (range 4 hours-20 days) and manifestations of the lower limbs prevail (present in all cases).
From our systematic review, it seems to emerge that post-vaccine cutaneous small-vessel vasculitis are more frequent for inactivated vaccines, however our clinical case is secondary to vaccination with mRNA vaccine, described in literature.

In all cases examined, however, cutaneous vasculitis observed after COVID-19 vaccination have a good prognosis and are self-limited. In particular, no therapy or only steroid therapy (sometimes topical, sometimes systemic, sometimes in combination), is sufficient.

5. Conclusion
The case described presents the particularity of the onset of small vessels cutaneous vasculitis after Covid-19 and influenza vaccination.

The emergence of cutaneous vasculitis purpura post Covid-19 vaccination generally suggests a good prognosis with self-resolution, though the low number of cases examined in the literature does not allow to draw conclusions. Also our case presented a favorable course with clinical resolution with the help of topical steroid therapy only, confirming the apparent good prognosis.

Further investigations are essential both in the etiopathogenetic field, both in the clinical setting, to confirm the association between cutaneous vasculitis and vaccination and to confirm the favorable prognosis. Indeed it is important to know any possible adverse events of Covid vaccination to improve mostly patient safety.

Compliance with ethical standards
Disclosure of conflict of interest
No conflict of interest/Competing interests.

Statement of informed consent
Patients gave written consent to the publication.

Availability of data and material (data transparency)
Yes.

Authors’ contributions
All authors contributed equally

References


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