Transient cryoglobulinaemic vasculitis following ChAdOx1 nCoV-19 vaccine

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SUMMARY

Cryoglobulinaemic vasculitis is an immune-complex-mediated, systemic inflammatory syndrome usually involving small-to-medium vessels due to precipitation of cryoglobulins at <37°C. It can involve any organ but most commonly affects the skin. Associated conditions include infections (hepatitis C and HIV), haematological disorders (chronic lymphocytic lymphoma, monoclonal gammopathy of uncertain significance and multiple myeloma), autoimmune conditions (systemic lupus erythematosus and Sjogren syndrome) or as a complication following vaccination (influenza, pneumococcal and hepatitis B vaccines). Biochemical hallmarks include detection of serum cryoglobulin with low C4 levels. We describe a case of previous healthy patient with transient cryoglobulinaemic vasculitis after first dose of ChAdOx1 nCoV-19 vaccine (AstraZeneca/Oxford).

CASE PRESENTATION

A woman in her 50s, with no prior medical history, attended the ambulatory care clinic with a 2-day history of bilateral lower limb rash. It initially started around ankles, then gradually spread proximally to involve thighs. She denied any sick contacts, had no fever, neck stiffness or photophobia and had no history of respiratory or gastrointestinal symptoms. No new medications were recently commenced, including over-the-counter medicines and supplements. However, she had received her first dose of intramuscular ChAdOx1 nCoV-19 (AstraZeneca/Oxford) vaccine 9 days prior to the onset of the rash. She reported mild myalgia and low-grade fever after vaccination, which lasted only 24 hours.

Physical examination was normal except for bilateral palpable purpuric rash up to her thighs (figure 1), not extending above the waist.

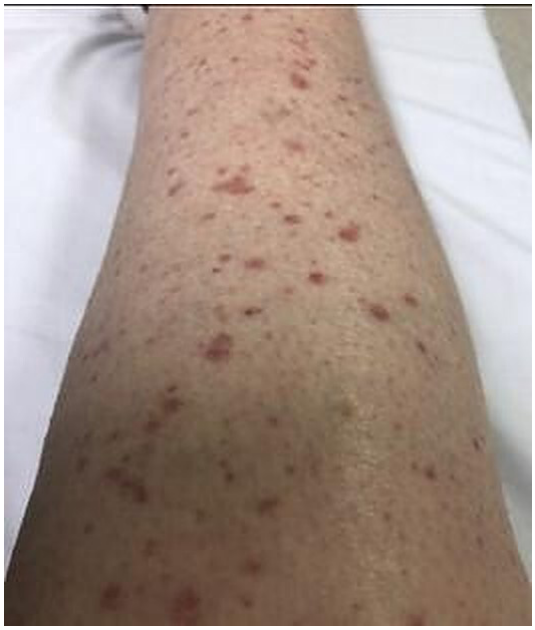

Figure 1 Skin rash.

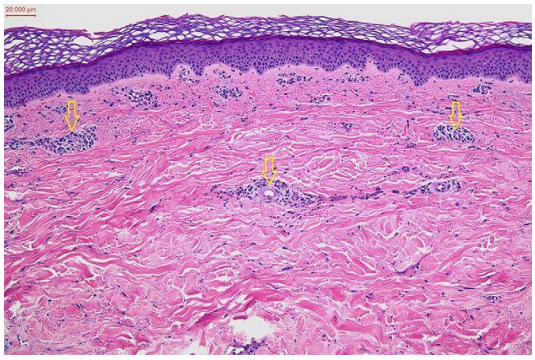

Figure 2 Medium power microscopy shows several upper dermal vessels (yellow arrows) with perivascular inflammation (H&E, ×100).

INVESTIGATIONS

Blood tests on presentation showed normal full blood count and renal function, with markedly low C4 level of 0.04 g/L (reference range 0.16–0.52) with normal C3 level, a mildly elevated rheumatoid factor of 20 kU/L (<14), CRP 5.6 mg/L (<5.0) and ESR 26 mm/h (1–15). Low level cryoglobulin (1+) was also detected, which was unable to be characterised on immunofixation. Screening for other causes of cryoglobulinaemia, including antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-hepatitis C antibody and hepatitis B surface antigen, were all negative. Skin biopsy included epidermis, dermis and a narrow rim of subcutis. It demonstrated a leucocytoclastic vasculitis pattern mainly involving the upper dermal small vessels (figure 2) and characterised by a perivascular infiltrate of neutrophils with scattered karyorrhectic debris associated with swollen vascular endothelial cells and perivascular red blood cell extravasation (figure 3).

OUTCOME AND FOLLOW-UP

The patient's symptoms resolved over the next 4 weeks without any treatment. Repeat blood tests after 4 weeks showed complete normalisation of C4 and rheumatoid factor. Cryoglobulins were not detected on repeat testing, indicating this was

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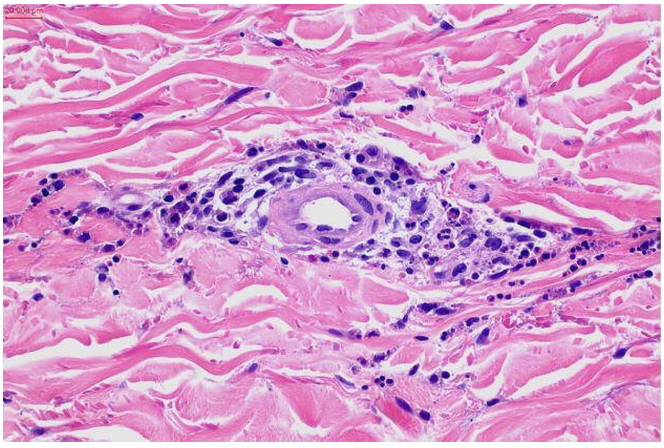

Figure 3 A high power microscopic image shows a dermal blood vessel with perivascular neutrophils and karyorrhectic debris associated with endothelial swelling (H&E, ×400).

a transient phenomenon. Interestingly, 12 weeks following her AstraZeneca/Oxford vaccine dose, the patient received the Pfizer SARS-CoV-2 vaccine without any significant adverse effects or abnormal laboratory results. A second dose of the Pfizer vaccine was also tolerated a further 3 weeks later. Based on the timing of vaccination and onset of clinical signs, in combination with the laboratory results and the absence of other identifiable causes, vaccine-induced cryoglobulinaemic vasculitis appears to be the most likely cause of our patient's presentation.

DISCUSSION

SARS-CoV-2 is a positive-sense single-stranded RNA virus and is the cause of COVID-19. The surface spike (S) protein facilitates entry into the human cell by binding to human angiotensin-converting enzyme 2 receptors through its receptor-binding domain, leading to fusion of the virus-host cell membrane and transfer of viral RNA into the host cell.[1] This S protein is the main target for many vaccines[2] and therapeutic agents.

COVID-19 was declared a global pandemic on 11 March 2020 and since then has affected almost 450 million people with over 6 million deaths worldwide as of March 2022.[3] Deaths typically result from severe respiratory disease,[4] multiorgan failure[5] and secondary haemophagocytic lymphohistiocytosis or inflammatory cytokine syndrome.[6]

Multiple SARS-CoV-2 vaccines were rapidly developed in response to this unprecedented humanitarian and economic crisis. Oxford University and AstraZeneca developed a viral vector vaccine using a modified DNA adenovirus. The modified adenovirus vector contains genes encoding the SARS-CoV-2 S protein, which is then produced once the vector is inside the cell. The S proteins then trigger a targeted immune response.[7] The initial studies reported the efficacy of a two-dose primary course at preventing symptomatic COVID-19 to be 70%–76%. Efficacy of this vaccine against variants such as Delta and Omicron is reported to be lower. The most common side effects reported were pain and swelling at the injection site, fever, fatigue, myalgia, arthralgia and headache. There are also case reports of rare side effects including anaphylaxis, coagulation disorder (vaccine-associated immune thrombotic thrombocytopenia) and immune mediated reactions including Guillain-Barre syndrome.[8]

Cryoglobulinaemic vasculitis is a rare condition and classified into three subgroups depending on immunoglobulin composition. Type I cryoglobulins are monoclonal immunoglobulins, primarily IgG or IgM. Type II cryoglobulins consist of monoclonal IgM (with rheumatoid factor activity) and polyclonal IgG, while type III cryoglobulins are polyclonal IgM and IgG. These immunoglobulins precipitate at <37°C and cause a spectrum of disease including hyperviscosity syndrome and immune-mediate disorders.

Cryoglobulinaemic vasculitis has been reported after vaccination, including influenza and pneumococcal vaccine.[9] The exact mechanism of vaccine-induced cryoglobulinaemic vasculitis is unknown. Cases of leucocytoclastic vasculitis have been reported following several of the SARS-CoV-2 vaccines, including the AstraZeneca/Oxford vaccine.[10] However, cryoglobulinaemia and cryoglobulinaemic vasculitis appear to be very rare.[11]

The Australian COVID-19 vaccine programme commenced in February 2021, and by March 2022 over 19.5 millions Australians (94.6% of people aged over 16 years) have received at least two doses of a COVID-19 vaccine.[3] In Australia, there are processes in place at both state and national levels for health departments to collect data regarding adverse drug reactions, including reactions to the COVID-19 vaccines.

While global strategies to stop the spread of the SARS-CoV-2 virus include social distancing, hand hygiene and development of novel therapies, widespread vaccination remains one of the key interventions to decrease the transmission of virus, reduce the risk of severe disease and death from infection, and also minimise the risk of further variants of concern emerging.[12 13] However, the safety of these vaccines must continue to be monitored closely and adverse reactions should be reported to appropriate authorities.

Learning points

- Cryoglobulinaemic vasculitis has been previously reported after pneumococcal, influenza and pertussis vaccines.
- Like other vaccines, COVID-19 vaccines may be associated with immune-mediated reactions including leucocytoclastic and cryoglobulinaemic vasculitis.
- With recent development of SARS-CoV-2 vaccines in response to the global COVID-19 pandemic, rigorous monitoring and reporting of potential side effects should be undertaken to ensure vaccine safety.
- Cryoglobulinaemic vasculitis can manifest as mild or severe disease, depending on the extent of organ involvement. It can be self-limiting without treatment, whereas severe cases may require immunosuppressive therapy such as corticosteroids.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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