Behçet's-like adverse event or inaugural Behçet's disease after SARS-CoV-2 mRNA-1273 vaccination?

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Running title:

Behçet's disease after SARS-CoV-2 mRNA vaccination

Key message: We describe a Behçet's-like adverse event or new-onset Behçet's disease occurring shortly after a SARS-CoV-2 mRNA-1273 vaccination.

Dear Editor,

Vaccination represents an essential step in controlling the actual SARS-CoV-2 pandemic. While mRNA-vaccines are generally well tolerated, they may rarely trigger flares or unveil auto-inflammatory diseases. Reports of systemic immune-mediated adverse effects after SARS-CoV-2 vaccination are limited and in most cases describe patients with known underlying conditions [1]. Here we report a case of a new-onset Behçet's disease (BD) or a BD-like adverse event occurring 15 days after a second shot of the SARS-CoV-2 mRNA-1273 vaccine.

A woman in her late 20s, Caucasian, from Argentina, only known for polycystic ovary syndrome, presented to the emergency department with a 1-week history of general malaise and a first episode of painful oral and genital ulcers. In the few days prior to admission, she also developed skin pustules on the trunk and in the face, as well as sore throat and unusual bi-temporal and retro-orbital headaches. She did not take any medication. Family history of autoimmune or autoinflammatory diseases, and risk factors for sexually transmitted diseases were absent. While the first dose of mRNA-1273 vaccine was well tolerated, she developed shortly after the second dose a 48-hour fever, transient local pain and axillary adenopathy, followed 15 days later by the non-self-limiting symptoms that led to her hospitalisation. At admission, she showed low-grade fever, multiple painful oral and genital ulcers (Figure 1A & B) and pseudofolliculitis (Figure 1C). Cardiac, respiratory, articular, neurologic, and abdominal examinations were normal. Ophthalmologic examination revealed bilateral papillary oedema, without any other ocular lesions. Initial laboratory work-up showed mild leucocytosis, with neutrophilia and moderate lymphopenia. C-reactive protein and blood sedimentation rate were elevated (Supplementary Table S1, available at *Rheumatology* online).

Cerebral MRI showed intracranial hypertension without other pathologic finding. The lumbar puncture had elevated opening pressure (27 cm H_2O) and cerebrospinal fluid showed mild lymphocytic pleocytosis and slight elevation of proteins, consistent with aseptic meningitis, as microbiological and serological analyses remained negative (Supplementary Table S1, available at *Rheumatology* online).

Based on the clinical presentation, BD was suspected, and the patient was started on colchicine 2 x 0.5mg/day, with moderate improvement of skin lesions and oral ulcers. Due to persistent headache and painful genital ulcers, prednisone 1 mg/kg/day was started on the 5th day of admission, leading to a rapid resolution of symptoms. Secondary laboratory work-up showed low-titer anti-nuclear antibodies, without antibodies to extractable nuclear antigen or chromatin. The remaining of the analyses was within normal range (Supplementary Table S1, available at *Rheumatology* online). HLA-B*51 was absent.

At the 1.5-month follow-up visit, the mucocutaneous lesions had completely healed. However, the patients still complaint of retro-orbital pain, associated with eyestrain. Ophthalmologic examination and a cerebral MRI showed persistent papillary edema and intracranial hypertension findings, respectively. Furthermore, two spots of retinitis were identified in the left eye. We therefore added azathioprine and acetazolamide to her treatment.

Our patient exhibited clinical features of BD (6 points using the International Criteria for BD). In the absence of recurrence, BD is not certain, but can be considered probable [2]. Indeed, with the persistence of an intracranial hypertension and the apparition of a retinitis, BD seems more likely. Absence of HLA-B*51 is consistent with mucocutaneous BD phenotype more common in young female patients [3]. Although unspecific, elevated CRP can be seen in active neuro-BD [4]. A recent study described 27 cases of inflammatory disease flare after SARS-CoV-2 mRNA vaccination. 17 of them experienced flares of a known inflammatory disease (including four BD flares) and ten new-onset inflammatory disease, none of which was reported to be BD. In this study, median time to onset of systemic symptoms after vaccination was 4 days [1]. However, the observed range was up to 25 days, which is in line with our own observation. Flares of BD have also been described after the 23-valent polysaccharide pneumococcal vaccine [5], while other classic vaccines are regarded as safe in this setting. Currently, SARS-CoV-2 vaccination is recommended in BD, although it is advisable to not immunize patients with a significant flare [6].

To the best of our knowledge, we report the first case of a clinical presentation consistent with inaugural BD or a BD-like adverse event following mRNA vaccination. The close temporal association of such a rare clinical picture and the exclusion of alternative diagnoses makes the vaccine a plausible trigger of the disease flare, even if causality cannot be demonstrated. Our report stresses the importance to consider, recognize and treat accordingly BD-like adverse event or new-onset BD in people receiving SARS-CoV-2 mRNA-1273 vaccination.

Authors' contributions

FT wrote the manuscript. LC informed the patient and obtained her written consent. FT, LC, BF, DG, CR and MM followed the patient in the clinics and reviewed the manuscript. BF and MM took the clinical pictures.

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Consent: The patient gave her written consent for the use of her anonymized clinical data and pictures for publication.

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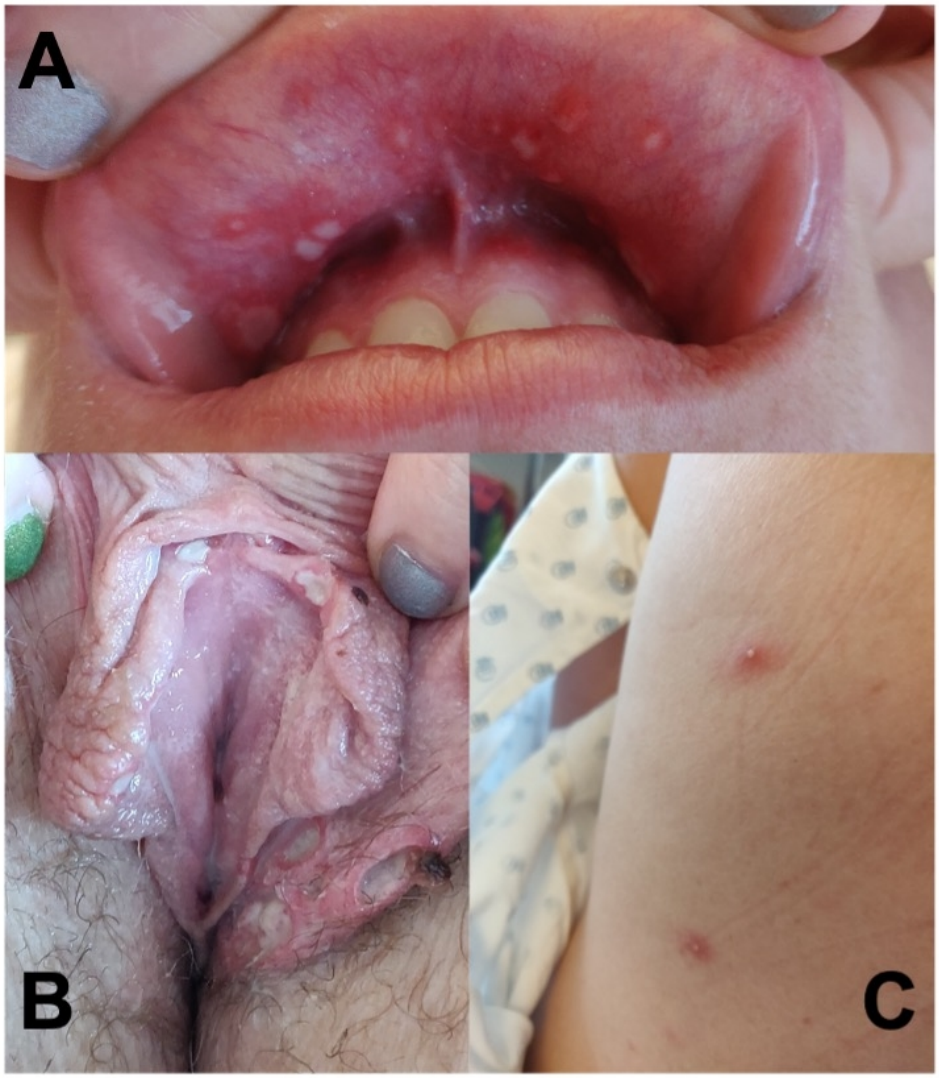
Figure 1. Clinical manifestations of the patient. (A) Oral ulcers, lying mainly on the inferior and posterior internal lips as well as on the soft palate, (B) genital lesions were up to 1.5 cm of diameter and located both on external and internal labia, and within the vagina, (C) skin pseudofolliculitis was limited to the thorax, the back (shown here) and the face.



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