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Editorial

EDITORIAL

Can SARS-CoV-2 vaccinations induce auto-inflammatory diseases?

Recently, Tagini *et al.* [1] elaborated on symptoms occurring 15 days after a second sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccination in a young woman presenting with new-onset symptoms compatible with Behçet's disease (BD). The obvious question arises whether these observations have a casual relation with the vaccination.

Causality of immune-mediated inflammatory diseases after vaccination expressed as proven adverse events following immunization (AEFIs) can be evaluated according to a World Health Organization–adapted comprehensive four-step algorithmic process [2]. In this cross-sectional study of Israeli, British and American centres, several inflammatory cases such as pericarditis, Henoch–Schönlein purpura, myasthenia gravis, multiple sclerosis and arthritis were related with coronavirus disease vaccinations. The assessment parameters require accurate diagnosis, vaccine administration before immune-mediated inflammatory diseases within a plausible time window and evidence for other causes and known causal associations [2]. In this light, Tagini *et al.* [1] support the causality of their findings in the reported case. To refute this theory and to anticipate future autoinflammatory AEFIs it is important to evaluate this hypothesis and correlate it with what is known about the immune-pathophysiological background of autoinflammatory diseases in handling danger signals such as vaccinations.

First, is the diagnosis of BD correct? The criteria of the International Society for BD require recurrent oral ulcers for at least three periods within 1 year accompanied by two of the following findings: genital ulcers, erythema nodosum–like skin lesions or pseudofolliculitis, uveitis and a positive pathergy test [3]. The authors state that the patient does not fulfil the criteria for BD because there were not three successive periods of oral ulcers. The BD-related symptoms (oral and genital ulcers and pseudofolliculitis) responded swiftly to first-line therapy for intracranial hypertension with papillary oedema. There were no intracerebral or meningeal inflammatory lesions detected by MRI, but pleocytosis in the spinal fluid indicated (autoinflammatory) meningeal inflammation. Other sensorimotor failure did not occur, which is unusual for neuro-BD [4]. After 6 weeks, intracranial hypertension symptoms persisted and azathioprine and acetazolamide were added for ocular inflammation (iritis). In general, BD symptoms swiftly resolve after steroid therapy and patients do not usually present with elevated CRP >10 times the normal values, in contrast with the reported case [3]. Furthermore, new ocular symptoms during steroid treatment are uncommon. However, since all other diagnoses were correctly excluded and the complaints resolved after additional BD-directed therapy, there is no alternative diagnosis. Therefore the diagnosis of BD, or BD-like symptoms, even though in this case it might be rather atypical, appears valid. It is of importance to observe whether the symptoms remain therapy dependent or resolve spontaneously in time.

Another interfering factor might be that these observations are merely coincidental. Hence, what are the chances to diagnose new BD patients in Switzerland? BD is an autoinflammatory condition and is very rare in Switzerland, occurring with a prevalence of 4/100 000 [5]. Originating from Turkey, prevalence figures meander towards China following the old Silk Route and are associated with HLA-B51. Further westward, the disease disperses from the Mediterranean countries towards South America, ranging from 370/100 000 to $\sim$1/1.000 000 in Turkey and America, respectively. Incidence figures of BD are scarce. In Western countries, annual incidence rates of 3.8/1 000 000 are reported. Prevalence figures in the USA are comparable to those of Switzerland [3]. Those figures would therefore indicate that in July 2021 among the fully vaccinated Swiss population at the time of patient presentation (i.e. 1 July 2021), about one new patient would be diagnosed with BD ($\sim$3.5 million fully vaccinated Swiss $\times$ 3.8/1 000 000 divided by 12 months). This rough estimate does not correct for ages or ethnicity, but the age at onset of the reported patient fits in the normal range between the ages of 20 and 40 years in which new BD patients are diagnosed [3]. Taking these figures into account, the chances of a coincidental appearance of BD 15 days after a vaccination cannot be ruled out.

This case would represent the first new-onset BD patient reported after SARS-CoV-2 vaccinations. There are reports of various autoimmune diseases such as SLE, hepatitis, Guillain–Barré syndrome and primary biliary cholangitis occurring either after SARS-CoV-2 infection or after SARS-CoV-2 vaccination [6]. BD is considered autoinflammatory, occurring after triggering a genetically susceptible host [3]. Except for pericarditis, a potential autoinflammatory disorder, there is only one AEFI in an autoinflammatory condition (sarcoidosis) reported after SARS-CoV-2 vaccination [2, 7]. Other autoinflammatory diseases such as Crohn's disease do not exacerbate and are not linked with SARS-CoV-2 vaccinations [8]. Interestingly, idiopathic pericarditis is an

autoinflammatory condition responsive to colchicine, which is standard BD therapy [2, 3]. It is likely that similar triggering mechanisms may be responsible for causing an autoimmune-mediated reaction in both situations. Mechanistically, triggering the immune system is linked to disturbed self-tolerance, cross-reactivity of the antibody to SARS-CoV-2 spike protein and nucleocapsid to various self-human antigens, leading to autoimmunity [6]. Also, cytokine-induced hyperinflammation via the transcription factor nuclear factor (NF)-κB may lead to autoinflammatory responses to vaccinations [7, 9]. After uptake of the mRNA vaccine it may stimulate Toll-like receptors, resulting in a cascade of intracellular processes activating an innate immunity–driven cascade of inflammasome platforms such as NF-κB. This pathway is strongly associated with pro-inflammatory cytokine-driven patterns seen in BD and related autoinflammatory conditions [3]. New-onset BD or disease flares are reported after other viral infections or vaccinations [10]. It remains unclear why reports on new-onset autoinflammatory disease after SARS-CoV-2 vaccination are scarce.

In conclusion, this report handles the onset of an atypical BD case after SARS-CoV-2 mRNA vaccination. A causative association remains obscure. Mathematically, the occurrence of BD could be purely coincidental. However, causative arguments include the immunopathophysiological nature of BD, previous reports of flares and new-onset autoimmune diseases after SARS-CoV-2 infections or vaccinations and the occurrence of new-onset BD after other vaccinations. This case might therefore herald reports on future SARS-CoV-2 infection or vaccination-related autoinflammatory cases. Whether this occurs in (genetically) predisposed patients who would have eventually developed autoinflammatory diseases at a later stage remains speculative. Even if there is any causative relation, figures remain extremely scarce and do not outweigh the benefit of the current vaccination strategies.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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