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CASE BASED REVIEW

Flare of adult-onset Still's disease following mRNA COVID-19 vaccination: a case report and review of literature

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Abstract

The upheaval caused by the coronavirus disease 2019 (COVID-19) pandemic has allowed to large population to use new vaccines urgently. Although vaccine development programs and available epidemiological data reassure us, there are concerns about specific risks associated with vaccinations in patients with autoimmune-autoinflammatory diseases. These patients have the potential to decrease humoral and cellular immune responses caused by biologic agents and develop an acute flare of underlying disease following vaccination. We herein present a rare case of a 49-year-old female with a flare of adult-onset Still's disease (AOSD) after the first dose of BNT162b2 mRNA COVID-19 vaccination. She had been diagnosed with AOSD 7 years earlier and had achieved remission with tocilizumab. This patient came to the emergency room with fever and nausea that occurred 4 days after the first vaccination. Based on laboratory results and clinical manifestations, we suspected AOSD flare and was treated with steroid pulse therapy. In this report, we also discuss possible mechanisms linking vaccination with a flare of AOSD. Considering the close time relationship between COVID-19 vaccinations and a flare of AOSD, physicians should be aware of adverse events from this new vaccination and evaluate the benefits and risks of vaccination for each patient.

Key Point

• *COVID-19 vaccination may cause an AOSD flare in patients who are in remission with tocilizumab.*

Keywords Adult-onset Still's disease · Biologic agent · COVID-19 vaccination · Disease activity · Flare

Introduction

The upheaval caused by the coronavirus disease 2019 (COVID-19) pandemic has raised the need for effective vaccines worldwide and therefore enabled vaccine use within 1 year of the emergence of the new virus [1]. Urgent use of vaccines to form herd immunity before the collapse of public health and the global economy has been authorized to large populations [2]. The safety, immunogenicity, and efficacy of the vaccine have been extensively studied through computer simulations, animal experiments, and human clinical trials [3]. However, establishing safety for all subgroups, including those with underlying diseases and young ages, remains a challenge to be solved [4]. Among those with underlying diseases, particularly in patients with autoimmune-autoinflammatory diseases (AIAIDs), may have specific risk and benefit profiles for vaccines. Given both the pathogenic mechanisms of immunological diseases and the immunosuppressive agents used in treatment, COVID-19 vaccination requires special consideration to such patients [5].

An increasing number of biologic therapies are being investigated and approved for treatment of various AIAIDs.

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The development of biologic therapies includes monoclonal antibodies targeting cytokines such as tumor necrosis factors (TNF) or interleukins (IL) and new novel small molecules which inhibit signal transduction via the intracellular pathways of inflammation [6]. Although guidelines have been proposed to recommend vaccination for patients with AIAIDs on these biologic agents, the impact of the vaccine is still controversial and relevant safety data are scarce [7, 8]. There are two main concerns regarding COVID-19 vaccination in patients with AIAIDs: the concerns about decreased humoral and cellular immune response caused by biologic agents and the potential to develop an acute flare of underlying disease. Cases related to the latter concern have also been reported in several AIAIDs [9].

Here, we report the case of a patient who developed a flare of adult-onset Still's disease (AOSD) who maintained remission with tocilizumab after her first vaccination with BNT162b2 mRNA COVID-19 vaccine (Pfizer, Inc., and BioNTech).

Case description

A 49-year-old woman was first diagnosed with AOSD at the age of 42 years, when she presented with an evanescent skin rash, fever, liver enzyme elevation, hepatosplenomegaly, and arthritis. Tests for rheumatoid factor and antinuclear antibodies were negative. She was admitted to the hospital after 5 flare-ups a year with symptoms of fever, arthritis, and evanescent skin rash, despite aggressive therapy that included high levels of prednisolone (60 mg/day), methotrexate (MTX) (15 mg/week), cyclosporine (100 mg/day), and azathioprine (100 mg/day). She was refractory to corticosteroid therapy, MTX, and azathioprine; therefore, monthly infusions of tocilizumab (TCZ; 400 mg) were initiated for 12 months after the diagnosis of AOSD.

This treatment appeared to be effective for 76 months, without any flares, until she presented to our emergency ward with complaints of mild fever, nausea, and myalgia that had persisted for 16 days. These symptoms developed 4 days after the first dose of the mRNA COVID-19 vaccine, and 1 week before the emergency room visit, TCZ was administered as scheduled and prednisolone (30 mg/day) increased to moderate dose, but the symptoms persisted. On admission, her vitals were within normal ranges. The laboratory data were as follows: white blood cell count, 7900 per mm^3 (76% neutrophils and 16% lymphocytes) (reference, 3400−10,600 per mm^3); hemoglobin level, 7.9 g/dL (reference, 10.7−15.3 g/dL); erythrocyte sedimentation rate (ESR), 2 mm/h (reference, 0−25 mm/h); C-reactive protein (CRP), 0.06 mg/dL (reference, 0−0.5 mg/dL); lactate dehydrogenase (LDH), 1499 U/L (reference, 100−200 U/L); and ferritin, 27,586 ng/mL (13−150 ng/mL). Anti-nuclear antibody and rheumatoid factor were negative. Blood cultures, urine analysis, and real-time polymerase chain reaction test for COVID-19 were all negative. No specific abnormalities were found on chest and abdominal computed tomography. Infection and malignancies were excluded by clinical evaluation, laboratory, and radiologic findings. Based on these results, we found that her symptoms were attributed to an AOSD flare after vaccination. Despite increased steroid administration, high-spiking quotidian fever, hemoglobin decrease, and ferritin elevation worsened, she was immediately administered IV corticosteroids (methylprednisolone 500 mg) for 3 days. Immediately after steroid treatment, her hemoglobin level and other laboratory findings recovered (Fig. 1). The prednisolone dose was maintained at 30 mg/day for a further 2 weeks. After that, she received infusions of TCZ (400 mg) by reducing prednisolone to 20 mg/day and maintained TCZ (400 mg) IV at monthly intervals with MTX (10 mg/week) while gradually reduced prednisolone dose.

Search strategy

A systemic search of the publication literature on the electronic bases Medline/PubMed, Scopus, and EMBASE was conducted using the following keywords: "COVID-19 vaccination," "SARS-CoV-2 vaccination," "adult-onset Still's disease," "flare-up," "relapse," "autoinflammatory disease," "tocilizumab," also including their abbreviations. Our literature review was searched from November 2019, when it is estimated that COVID-19 first occurred, and was last updated on November 1. Each article was analyzed to identify eligibility criteria and their relevance to this study. We included only the case reports for adult patients written in English. The exclusion criteria included publications of reviews, letters, or abstracts only; and different languages other than English. The flowchart of the study selection process is shown in Fig. 2. After excluding non-relevant papers and duplicates, fourteen articles met our searching inclusion criteria: two cases of AOSD flare-up after COVID-19 vaccination (Table 1), six cases of new-onset of AOSD after COVID-19 vaccination (Table 2), and six cases of new-onset or flare-up of AOSD after other vaccinations (Table 3).

Discussion

AOSD is a systemic auto-inflammatory disorder of unknown etiology characterized by high spiking fever, arthritis, an evanescent salmon-colored rash, and laboratory abnormalities including leucocytosis, high serum ferritin levels, elevated liver enzymes, and elevated acute phase reactants (APRs) such as ESR and CRP [23]. The pathogenesis of AOSD remains unclear; however, dysregulation of the inflammasome complex with overproduction of pro-inflammatory cytokines (e.g., TNF-α, IL-1, IL-6, IL-18,

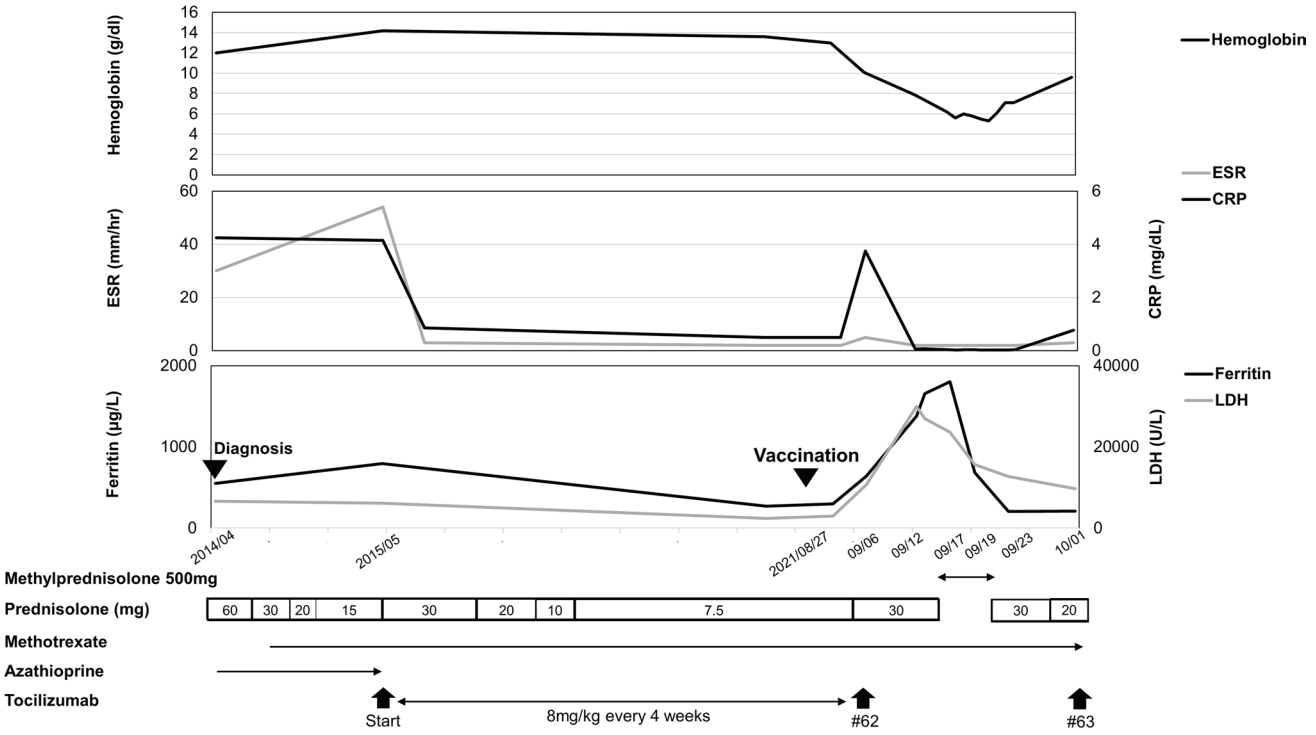

Fig. 1 Changes of laboratory findings according to treatments and vaccination. Hemoglobin levels were declined significantly after first vaccination with mRNA coronavirus disease 2019 (COVID-19) vaccine

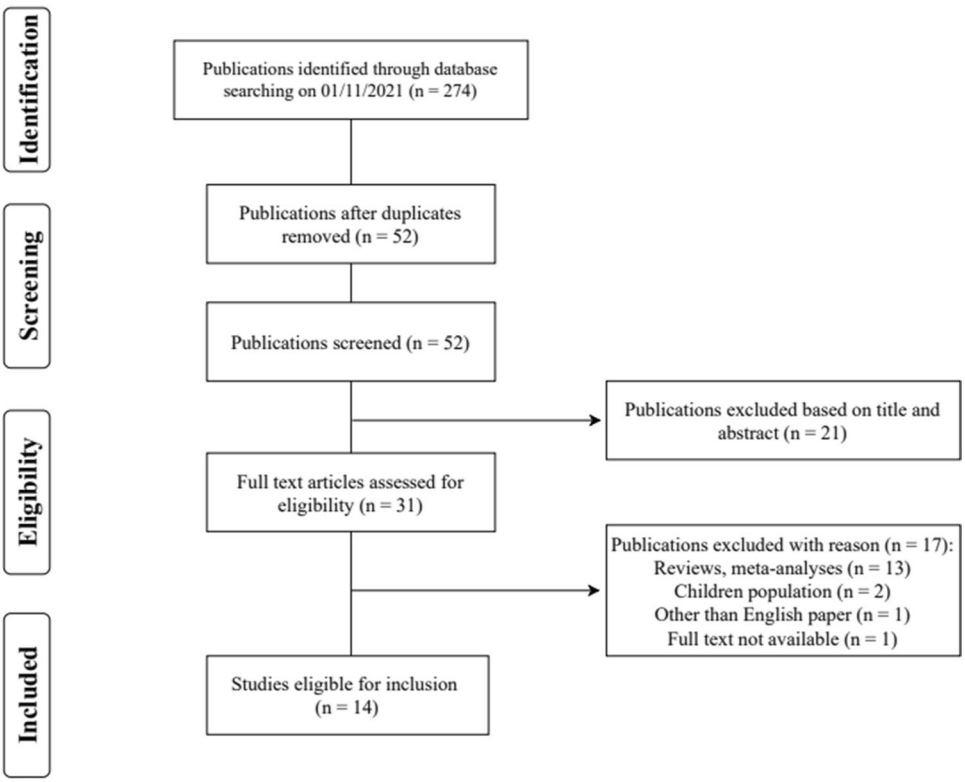

Fig. 2 Flowchart of the study selection process

Table 1 Cases of disease flare of AOSD after COVID-19 vaccination

Sex/age	AOSD duration	Type of vaccine/manufacturer	Symptom onset time after vaccination	Presenting symptoms	Relevant laboratory results	Treatment before event	Treatment for flare	Country [Ref]
F/37	13 years	mRNA vaccine/BNT162b2 (Pfizer)	A few days after the second dose	High-grade fever Salmon-pink eruption Polyarthritis Sore throat	Elevated CRP and LDH Negative RF and ANA Lymphadenopathy on CT	A drug-free remission status for the previous 2 years	Tocilizumab subcutaneously at 162 mg/m^2 weeks	Japan [10]
F/34	22 years	Viral vector vaccine/ChAdOx1 nCoV-19	7 days after the first dose	High-grade fever Salmon-pink eruption Sore throat Pleuritic chest pain	Leukocytosis with elevated CRP and ESR High serum ferritin Negative ANA Minimal pericardial effusion	Low disease activity with etanercept and low-dose glucocorticoid for 14 years	Methylprednisolone pulse 125 mg for 3 days Tocilizumab 8 mg/kg every 2 weeks for 2 months	South Korea [11]

AOSD adult-onset Still's disease, *COVID-19* coronavirus disease 2019, *Ref* reference, *mRNA* messenger ribonucleic acid, *CRP* C-reactive protein, *LDH* lactated dehydrogenase, *RF* rheumatoid factor, *ANA* anti-nuclear antibody, *CT* computed tomography, *SC* subcutaneous

and interferon-γ) appears to play a pivotal role [24]. Treatment using biologics targeting these cytokines, such as the IL-6 receptor antagonist TCZ and IL-1 receptor antagonist anakinra, has become an attractive therapeutic option in the recent years [25].

In the COVID-19 era, the role of inflammatory cytokines in the balance between virus clearance and hyperinflammation mediating severe diseases is being highlighted. Uncontrolled and increased release of pro-inflammatory cytokines and impairment of virus clearance led to cytokine storms, creating a background for severe COVID-19 [26]. Macrophage activation syndrome along with hyperferritinemia and fever, which are induced in severe COVID-19 courses, shares striking features of the cytokine storm-associated mechanisms in AOSD, suggesting that COVID-19 and AOSD have similar clinical and laboratory findings [27–29]. Indeed, evidence of a similar role in the highly efficient treatment for AOSD targeting interleukin is increasing in COVID-19 hyperinflammation [30]. Cytokine modulators were evaluated in clinical trials for COVID-19, and TCZ, an IL-6 inhibitor, is used as one of the options for cytokine storm treatment that causes multiple organ damage and death during COVID-19 [31, 32]. Recently, there was a case of treatment with the IL-1 receptor antagonist anakinra in a patient diagnosed with AOSD after recovering from a COVID-19 [33].

There have been some case reports in which a misdirected immune response against COVID-19 triggered the onset of AOSD [33, 34]. Theoretically, an innovative vaccine of COVID-19 may behave like an adjuvant, resulting in perturbations in immune system, acting as a potential trigger for AOSD. As of concern, several cases of flares of other AIAIDs [9, 35] or new diagnoses of AOSD due to COVID-19 vaccination have been reported [12–16]. On the other hand, to the best of our knowledge, there have been only two cases of flare up of AOSD reported following COVID-19 vaccination [10, 11]. There was one case of flare of AOSD after the second dose of COVID-19 mRNA vaccine was reported in Japan [10]. This patient had repeated remissions and relapses of AOSD but was relieved with low dose of steroids and achieved drug-free remission status over the past 2 years before vaccination, and improved symptoms by treating with TCZ for a flare that occurred after vaccination. In another case, AOSD flared after the first dose of ChAdOx1 nCov-19 vaccination while maintaining low disease activity of AOSD with etanercept, and symptoms significantly improved as etanercept was change to TCZ [11].

Contrary to the reported cases in which flare up of AOSD was treated with TCZ, it is noteworthy that in our case, AOSD was flared even though TCZ was administered 10 days after the first dose of vaccination. Unlike other biologic agents that decrease the humoral response to vaccines, TCZ induces a strong anti-inflammatory response while sustaining the protective humoral response; thus, it is not recommended to adjust the administration schedule according to COVID-19 vaccination, and our patient received TCZ as scheduled [36]. Given the close temporal relationship between vaccination and onset of symptoms despite TCZ preventing the cytokine storm and ruling out other infections and malignancies, we concluded that vaccination against COVID-19 may have triggered the occurrence of flare of AOSD.

Table 2 Cases of new-onset of AOSD after COVID-19 vaccination

Sex/age	Type of vaccine/ manufacturer	Symptom onset time after vaccination	Presenting symptoms	Relevant laboratory results	Treatment for AOSD	Country [Ref]
M/36	Viral vector vaccine/ ChAdOx1 nCoV-19	4 days after the first dose	High-grade fever Evanescent rash Chest pain	Leukocytosis with elevated CRP and ESR High serum ferritin	Methylprednisolone 1 mg/kg IL-1 receptor antagonist anakinra (100 mg daily)	Italy [12]
M/22	mRNA vaccine/ BNT162b2 (Pfizer)	13 days after the first dose	High-grade fever Chest pain Maculo-papular eruption Arthritis	ST elevation on ECG High serum ferritin	Methylprednisolone pulse 1 g for 3 days IV immunoglobulins 2 g/kg IL-1 receptor antagonist anakinra (100 mg daily)	Romania [13]
M/43	mRNA vaccine/ BNT162b2 (Pfizer)	10 days after the second dose	High-grade fever Macular rash Arthritis Sore throat	Leukocytosis with elevated CRP Increased LDH Bilateral pleural effusion Negative RF and ANA	Methylprednisolone pulse 1 g for 3 days	Israel [14]
F/56	mRNA vaccine/ BNT162b2 (Pfizer)	7 days after the second dose	High-grade fever Arthritis Sore throat Chest pain	Leukocytosis with elevated CRP High serum ferritin Increase liver enzymes Negative RF and ANA	Methylprednisolone 1 mg/kg	Israel [14]
F/45	mRNA vaccine/ mRNA-1273 (Moderna)	5 days after the second dose	High-grade fever Sore throat Myalgia	Leukocytosis with elevated CRP and ESR Elevated cardiac biomarkers Lymphadenopathy on CT Bilateral infiltrates on chest X-ray	Methylprednisolone 1 mg/kg	USA [15]
F/36	mRNA vaccine/ BNT162b2 (Pfizer)	10 days after the first dose	High-grade fever Sore throat Arthritis	Leukocytosis with elevated CRP and ESR Splenomegaly and lymphadenopathy on CT Negative RF and ANA	Methylprednisolone pulse 1 g for 3 days Tocilizumab 8 mg/kg IV	South Korea [16]

AOSD adult-onset Still's disease, *COVID-19* coronavirus disease 2019, *Ref* reference, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IL* interleukin, *mRNA* messenger ribonucleic acid, *ECG* electrocardiogram, *IV* intravenous, *LDH* lactated dehydrogenase, *RF* rheumatoid factor, *ANA* anti-nuclear antibody, *CT* computed tomography

The mechanisms underlying AOSD flare-ups after vaccination have not yet been elucidated. A possible pathologic mechanism is that mRNA transcribes into spike glycoproteins after inoculation, and these proteins are displayed on antigen-presenting cells by molecular mimicry, leading to an acute immune response [37]. Another potential cause is that the mRNA vaccine acts as an adjuvant and stimulates innate immunity through endosomal and cytoplasmic immune receptors, such as toll-like receptors [38]. Moreover, one published data showed that BNT162b2 mRNA vaccines may induce a significant increase in IL-6, IL-15, and interferon-γ, which play an important role in the pathogenesis of AOSD [39]. We hypothesized that the occurrence of this event in our patient who was being treated with IL-6 inhibitor resulted in a flare of AOSD due to activation of cytokines other than IL-6 following the vaccination.

In this particular case, there are two main emphases on COVID-19 vaccination in patients with AOSD. First,

Table 3 New onset or flare-up of AOSD after several vaccinations

Sex/age	Pre-vaccine history of AIAIDs or comorbidities	New onset or flare-up	Type of vaccine	Symptom onset time after vaccination	Country [Ref]
M/66	No	New onset	23-valent pneumococcal polysaccharide vaccine	1 week after receiving vaccine	Israel [17]
F/73	No	New onset	Influenza	2 days after receiving vaccine	South Korea [18]
F/61	No	New onset	Influenza	NA	Japan [19]
F/20	No	New onset	Influenza	1 week after receiving vaccine	Thailand [20]
F/66	No	New onset and flare-up	Influenza	1 week after receiving vaccine	Japan [21]
F/38	No	New onset	Hepatitis A and B vaccination	10 days after receiving vaccine	France [22]

AOSD adult-onset Still's disease, *AIAIDs* autoimmune-autoinflammatory diseases, *Ref* reference, *NA* not available

regarding patients with TCZ-induced remission in refractory AOSD, it is necessary to consider an AOSD flare even if APRs are within the nearly normal range in the presence of suspected disease-triggering factors [40]. Since TCZ blocks IL-6, which is the major inducer of APRs, there may be no changes in APRs, as in this case. Therefore, other laboratory tests such as ferritin, LDH, WBC, and hemoglobin as well as the clinical features would play a major role in diagnosing AOSD flare in patients using TCZ. Second, COVID-19 vaccinations can cause new-onset AOSD and flares in patients in remission. There is a possibility of flare-up of the underlying disease due to the vaccination even in a long-term remission by maintaining the biologic agents, and similar situations may occur, especially in TCZ, which is also used as a treatment for COVID-19.

Although not all cases will be reported, COVID-19 vaccination induced new-onset or flare of AOSD cases are very low, given that nearly 40% of the world's population is fully vaccinated [41]. Fortunately, new-onset or flare of AOSD due to broadly used vaccines such as influenza, pneumococcal, and hepatitis vaccines were also rare [17–22]. In addition, a prospective cohort study has also been published that COVID-19 vaccine does not increase the risk of disease flare-ups in patients with autoimmune diseases [42]. The largest study reported on the use of viral vectors or mRNA vaccines in patients with AIAIDs on anti-IL-1/6 biologics also showed no serious concerns, such as hospital admissions and deaths, about COVID-19 vaccination [43]. However, the occurrence of hyperinflammation such as AOSD after any vaccinations, including COVID-19, should be recognized as a very rare possibility, as it can lead to life-threatening complications if treatment is not initiated immediately.

In conclusion, it is noteworthy that this patient is the first to report the development of AOSD flare after receiving the first dose of mRNA COVID-19 vaccinations. In addition, this is the first experience of disease flare in a patient with rheumatic diseases receiving TCZ. Although AOSD flares are rare and benefits of vaccinations outweigh the relatively small risks, physicians should inform patients of possible adverse effects from vaccinations, such as flare and should monitor them carefully to assist with worsening underlying diseases.

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Author contribution JWK, JYJ, CHS, and HAK contributed to the case presentation, data collection, and interpretation. JWK and HAK contributed to write the manuscript. All authors revised the manuscript and gave final approval for submission.

Data availability All available data are reported in the manuscript.

Code availability Not applicable

Declarations

Ethics The informed consent has been obtained from the patient. The protocol was waived because of retrospective nature.

Consent to participate Informed consent was provided by the patient.

Consent for publication Informed consent was provided by the patient.

Disclosures None.

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