Adult-onset Still's disease after mRNA COVID-19 vaccination presenting with severe myocarditis with acute heart failure and cardiogenic shock: a case report

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This article was published on 20 Mar 2023 at www.hkmj.org.

Hong Kong Med J 2023;29:162–4
https://doi.org/10.12809/hkmj2210110

Case report

We report the first case of adult-onset Still's disease (AOSD) following messenger ribonucleic acid (mRNA) coronavirus disease 2019 (COVID-19) vaccination presenting with severe myocarditis with acute heart failure and cardiogenic shock. A 72-year-old Chinese female, with history of subtotal thyroidectomy, hypertension, dyslipidaemia, and osteoporosis, developed gradual onset of fever, dyspnoea, sore throat, generalised arthralgia, malaise, and poor appetite 15 days after receiving the first dose of BNT162b2 mRNA COVID-19 vaccine, and was admitted 7 days after symptom onset in September 2021. Physical examination revealed fever, bilateral ankle oedema, and elevated jugular venous pressure. Polymerase chain reaction test for COVID-19 was negative on admission and throughout hospitalisation. Initial workup found increased C-reactive protein level of 182.3 mg/L (reference range, <7.6), severely elevated cardiac troponin I level of 7789 ng/L (reference range, <40) and N-terminal pro B-type natriuretic peptide level of 26 688 ng/L (reference range, <300), as well as deranged liver function. Chest X-ray showed progressive bilateral pulmonary infiltrates. Electrocardiography revealed fast atrial fibrillation with no other abnormalities including QRS or ST changes. Echocardiography showed severely reduced left ventricular ejection fraction of 20% with normal right ventricular function and no features of cardiomyopathy. Computed tomography of the thorax and upper abdomen did not show any features of malignancy, lymphadenopathy, interstitial lung disease or hepatosplenomegaly. Acute heart failure with reduced ejection fraction was diagnosed. The patient was prescribed empirical intravenous antibiotics and underwent septic workup with unremarkable results.

In view of the severe acute heart failure, the patient was transferred to the cardiac care unit of our hospital for further management on day 26 after vaccination. Significant investigation results are shown in the Table. Extensive viral panel tests (including enterovirus, influenza, and cytomegalovirus) were all negative. Shortly after transfer, the patient developed acute pulmonary oedema requiring 2 L/min oxygen and was treated with amiodarone, apixaban, and furosemide. On day 28 after vaccination, she developed cardiogenic shock requiring intensive care admission and was given noradrenaline and high-flow oxygen. Her atrial fibrillation persisted, and cardioversion was performed with consequent restoration of sinus rhythm.

The patient's cardiac function gradually improved as evidenced by recovering left ventricular ejection fraction upon echocardiography. After stabilisation, coronary angiogram with endomyocardial biopsy was performed on day 34 after vaccination. There was no evidence of significant coronary artery disease; histology showed mononuclear infiltrate and viral studies were negative. Nonetheless the patient had persistent quotidian fever of >39°C and arthralgia (bilateral shoulders, wrists, and proximal interphalangeal joints). She also developed a diffuse erythematous maculopapular rash over the trunk and limbs, with skin biopsy revealing interface dermatitis. She was transferred to the rheumatology unit. Blood test results showed neutrophilic leucocytosis (leucocyte count: 20.99×10^9/L), hyperferritinaemia level of 68 913 pmol/L (reference range, 29-337), deranged liver function, and elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein); autoimmune panel was unremarkable except for an antinuclear antibody titre of 1:80 (Table). Extensive septic workup after microbiologist consultation, including viral panel serology, was negative. Cardiac contrast magnetic resonance imaging on day 44 after vaccination showed diffuse myocardial oedema, consistent with myocarditis. Subsequent contrast positron

TABLE. Significant laboratory investigation results since the patient's transferral to the cardiac care unit taken on specific days after COVID-19 vaccination

	Day 26 Admission to the cardiac care unit	Day 28 Admission to the intensive care unit	Day 32 Onset of skin rash	Day 44 12 Days after onset of skin rash	Day 55 7 Days after initiation of oral corticosteroid	Day 62 5 Days after stepping up the dose of oral corticosteroid	Day 69 5 Days after starting valganciclovir, meanwhile the dose of oral corticosteroid was tapering down	Day 80 Date of discharge on oral prednisolone 40 mg daily
Leucocyte count, $\times10^9$/L (Ref range: 3.89-9.93)	20.44	39.16	20.99	23.01	10.70	6.17	4.25	3.40
Absolute neutrophil count, $\times10^9$/L (Ref range: 2.01-7.42)	19.06	36.42	19.90	21.97	9.23	4.91	2.95	2.58
Absolute lymphocyte count, $\times10^9$/L (Ref range: 1.06-3.61)	0.73	0.78	0.66	0.66	0.82	0.83	1.14	0.75
ESR, mm/hr (Ref range: <38)	-	-	100	-	91	79	73	77
CRP, mg/L (Ref range: <7.6)	224	-	150	79.3	42.6	20.1	16.0	5.1
Ferritin, pmol/L (Ref range: 29-337)	-	-	68 913	>224 720	105 751	69 760	>224 720	154 129
ALT, U/L (Ref range: 8-45)	116	137	44	136	60	91	143	197
AST, U/L (Ref range: 15-37)	112	149	57	180	115	76	192	133
Troponin T, ng/L (Ref range: <14)	621	825	266	127	78	-	-	-
NT-proBNP, ng/L (Ref range: <300)	-	-	-	6867	-	-	-	-
ANA titre	1/80	-	-	-	-	-	-	-
ANA pattern	homogeneous	-	-	-	-	-	-	-
Rheumatoid factor, IU/mL (Ref range: <15)	-	-	<12	-	-	-	-	-

Abbreviations: ALT = alanine transaminase; ANA = antinuclear antibody; AST = aspartate transaminase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; NT-proBNP = N-terminal pro B-type natriuretic peptide

emission tomography–computed tomography showed reactive lymphadenopathy but no features of malignancy.

The diagnosis of AOSD was made based on the Yamaguchi criteria and the Fautrel criteria.[1] The patient was treated with oral prednisolone 30 mg daily. Subsequent investigations revealed cytomegalovirus pp65 antigenaemia, hence valganciclovir was prescribed. Treatment was well-tolerated. Her fever gradually subsided, and leucocyte count and C-reactive protein level were normalised although serum ferritin, erythrocyte sedimentation rate and liver enzymes remained elevated. Three months after discharge, the patient was clinically well with prednisolone tapered down to 5 mg daily. Echocardiographic reassessment demonstrated full recovery with left ventricular ejection fraction of 60%.

Discussion

The pathogenesis of AOSD is hypothesised to be multifactorial and autoinflammatory, contributed by genetic predisposition, environmental triggers, and eventual immune dysregulation.[1] Infections can trigger AOSD, as pathogen-associated molecular patterns of pathogenic organisms or damage-associated molecular patterns from damaged host cells activate the innate immune system through pattern recognition receptors such as toll-like receptors on neutrophils and macrophages. In the presence of dysregulation, cytokine storm with overproduction of interleukin (IL)-6, IL-8, IL-17, tumour necrosis factor-alpha, IL-1β, and IL-18 can lead to the hyperinflammatory state of AOSD.[1] The mRNA COVID-19 vaccines also stimulate innate immune responses since the mRNA can act as both an immunogen encoding the viral antigen and an adjuvant that directly stimulates pattern recognition receptors, thus mimicking an infection.[2] Immune response after vaccination, such as production of cytokines, may trigger AOSD in a similar manner to infections.

To the best of our knowledge, there have not been reports of post–COVID-19 vaccine AOSD presenting with severe myocarditis with acute heart failure and cardiogenic shock. This case highlights the possibility of such an atypical presentation of post–COVID-19 vaccine AOSD, and the importance of monitoring for signs and symptoms of systemic inflammatory diseases in post–COVID-19 vaccine myocarditis patients (especially if the signs and symptoms are persistent). A high index of suspicion should be maintained and, if indicated, extensive workup carried out to establish a diagnosis so that appropriate treatment (such as corticosteroids or other immunosuppressants) can be offered.

Myocarditis is a rarely reported complication of AOSD.[1] Nonetheless all reports of post–COVID-19 vaccination AOSD to date, including our case, had some features of myocarditis.[3-5] Further studies are warranted to determine whether myocarditis is more likely to occur in post–COVID-19 vaccine AOSD, and whether post–COVID-19 vaccine myocarditis and post–COVID-19 vaccine AOSD are part of a spectrum of diseases.

Physicians should be reminded that both mRNA COVID-19 vaccine–related myocarditis and AOSD are exceedingly rare. As illustrated in this report, a comprehensive evaluation to exclude more common causes of heart failure and myocarditis should be performed first. Vaccine-related myocarditis and AOSD should be a diagnosis of exclusion, and all efforts should be made to not miss other possible aetiologies. It is important to emphasise that given the extreme rarity of such adverse reactions, the overall benefits of COVID-19 vaccines still far outweigh the risks for the general population.[3-5]

In conclusion, although exceedingly rare, severe myocarditis with acute heart failure and cardiogenic shock is a possible initial presentation of AOSD after mRNA COVID-19 vaccination. After exclusion of more common aetiologies, it is important to consider AOSD as one of the differential diagnoses in the presence of compatible features following COVID-19 vaccination, such that appropriate and timely workup and treatment can be offered.

Author contributions

Concept or design: All authors.
Acquisition of data: AKC Kan, WWY Yeung.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: AKC Kan.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

The patient was treated in accordance with the Declaration of Helsinki and has provided informed consent for all procedures and publication.

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