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Title:

Acute near-fatal multisystem inflammatory syndrome and fulminant myocarditis post ChAdOx1 nCoV-19 vaccination in a SARS-CoV-2 naïve individual

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Funding: Nil

Conflict of interest: Nil

Acknowledgment: Nil

A 38-year-old Korean man presented with a three-day history of fever, myalgia, sore throat and pleuritic chest pain, five days post his first ChAdOx1 nCoV-19 vaccination. He had no previous medical history and worked as a disability support worker. Within 12 hours the patient developed haemodynamic instability with persistent hypotension, tachycardia and type 1 respiratory failure. His pleuritic chest pain coupled with new ECG changes (hyperacute T waves and global ST elevation) and increasing cardiac-troponin I levels prompted cardiac catheterisation. Blood tests revealed anaemia 116g/L (135-180g/L), leukocytosis 21.6 x109/L (4.0-11.0 x109/L) with neutrophilia, mild coagulopathy INR 1.4 (0.9-1.2), elevated CRP 212mg/L (<5.0mg/L), and elevated cardiac-troponin I levels 3045nanog/L (<20nanog/L). Nasopharyngeal swab for SARS-CoV-2 GeneXpert and subsequent polymerase chain reaction were negative at admission and on repeat testing and pulmonary embolism was excluded with CT-pulmonary angiogram.

Cardiac catheterisation and transthoracic echocardiogram revealed normal coronary arteries and severe global left ventricular dysfunction: ejection fraction 20-30%. Progressive type 1 respiratory failure, non-invasive ventilation and orthopnoea precluded the patient from undergoing cardiac MRI. Endomyocardial biopsy (EMB) was performed and histology showed subendocardial infiltrate of neutrophils and lymphocytes consistent with acute neutrophilic myocarditis. Myocyte necrosis, eosinophils and giant cells were not detected within the specimen and PCR for CMV was negative (Figure 1). At the time of EMB the CRP was 496mg/L and ferritin 30,900microg/L (45-715microg/L). Extensive autoimmune and infection screening were negative except for serological evidence of previous exposure to CMV and EBV. The patient at this time lacked features of splenomegaly or significant hypertriglyceridemia (<2.9 mmol/L on separate occasions) and a Bone marrow aspirate and trephine showed reactive features and no significant haemophagocytosis.

This presentation preceded a publication from the Brighton Collaboration on Multisystem inflammatory syndrome associated with vaccination (MIS-V)[1], therefore he was diagnosed with a hyperinflammatory state with cardiac involvement likely temporally related to the ChAdOx1 nCoV-19 vaccination. Whilst this case was later found to be consistent with level-1 diagnostic certainty for MIS-V there is significant complexity and a precariousness around this possible diagnosis.

The patient was intubated on day 3 and treatment with three days of intravenous methylprednisolone 1g/d followed by high dose oral prednisolone starting at 120mg/d, and three days of intravenous immunoglobulin (IVIg) at 0.5mg/kg was commenced. Cardiac function improved rapidly but the hyperinflammatory state worsened with persistent fever and hyperferritinaemia to 152,000 microg/L. He was commenced on intravenous tocilizumab at 8mg/kg on day 12 of admission and was retreated on days 14, 19, 26 and 38. Ferritin reduced to 43,000 microg/L on day 24 and the patient was successfully extubated on day 23.

Recovery was further complicated on day 26 by CMV viraemia secondary to immunosuppression with transaminitis and an exacerbation of the hyperinflammatory state with fever, hyperferritinaemia 306,000 microg/L, pancytopenia and hypofibrinogenaemia. Further methylprednisolone and IVIg were required and due to the concern of tocilizumab contributing to hepatotoxicity, it was switched to subcutaneous anakinra 100mg daily. Patient was subsequently discharged on day 62 on anakinra 100mg daily, prednisolone 50mg/d and atovaquone for Pneumocystis jirovecii pneumonia (PCP) prophylaxis and has subsequently made a good recovery.

Following the severe illness the patient consented to further investigations inclusive of genetic analysis. Functional HLH testing was all normal (NK cell degranulation by CD107a, SLAM-associated protein and XIAP expression). Interestingly a single pathogenic variant in *PRF1* was demonstrated but thought insufficient to explain primary HLH in this individual given perforin deficiency is classically an autosomal recessive disorder presenting before the age of two. Whilst a contribution of this variant to a HLH/MAS illness cannot be completely excluded, it seems unlikely given that perforin expression via flow cytometry in this case was normal.

MIS-V is a recently reported very rare but potentially serious adverse effect of vaccines against SARS-CoV-2. The definition was established by the Brighton Collaboration in May 20211. Published case reports of MIS-V mostly demonstrate recovery with supportive measures and corticosteroid use, except in the setting of recent SARS-CoV-2 infection[2-6]. In this case report we describe an illness potentially consistent with severe, recalcitrant MIS-V refractory to steroid treatment requiring monoclonal antibody therapy in a SARS-CoV-2 naïve male, further complicated by CMV reactivation. Whilst satisfying the criteria for Level 1 MIS-V this case showed that a further exacerbation of the severe inflammatory syndrome was likely due (at least in part) to treatment complications. We are hopeful that this case may assist others in recognition of rare similar presentations and guide possible treatments.

References

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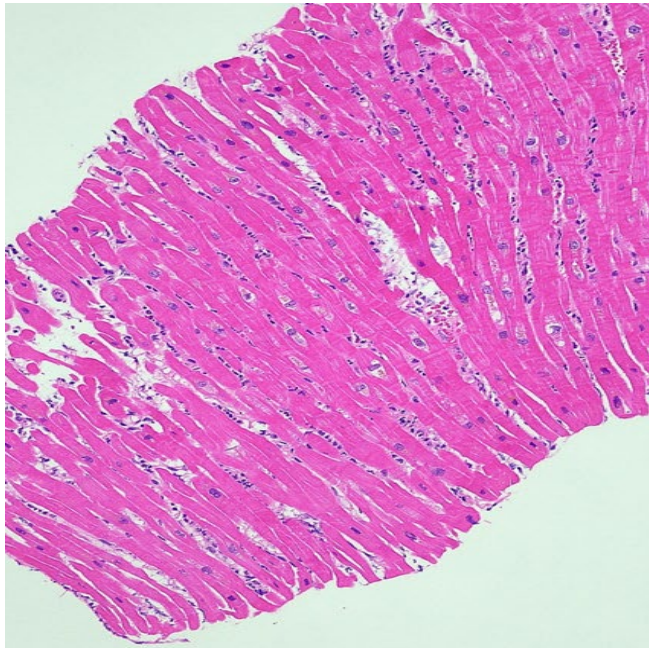
Figure 1: Endomyocardial biopsy



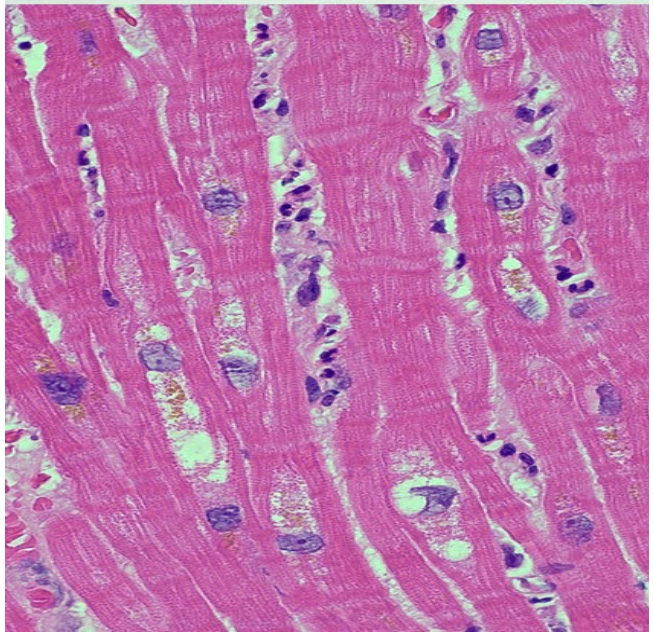


Figure 1: Endomyocardial biopsy of the patient showing interstitial neutrophils. No myocyte necrosis, giant cells, or viral inclusions.