Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The first case of AOSD after COVID-19 has recently been reported.[6] Systemic inflammation, unremitting fever, high serum ferritin, and a hyperinflammatory syndrome that induces major organ involvement characterise both AOSD[7] and severe COVID-19,[8] suggesting they might be triggered by the same mechanisms.

In the present case, the strong temporal association between the symptoms and COVID-19 vaccination prompted us to suspect a causal connection, since similar AOSD cases have been observed after vaccinations for influenza, hepatitis A, and hepatitis B.[9] However, we cannot exclude the possibility that the timing with regards to vaccination was coincidental. Possible pathogenic mechanisms might include high levels of spike protein production after vaccination, that also cause the immune system activation in COVID-19, suggesting that the inflammatory storm of AOSD can be triggered either by the infection or by the vaccination. Intrinsic adjuvant activity of adenoviral particles targeting innate immune cells and ultimately resulting in the production of type I interferon and multiple pro-inflammatory cytokines, might be another potential cause.[10] Finally, the role of vaccines-adjuvants such as polysorbate 80, which is present also in the influenza and hepatitis vaccines, might also be considered.[3] The response of COVID-19 to IL-1 blockade, known to produce substantial benefit in AOSD, further supports the hypothesis of a strict pathogenic connection between hyperinflammatory syndromes and severe COVID-19.[5]

We declare no competing interests. The patient provided informed consent to publish this case.

*Flavia Leone, Pier Giacomo Cerasuolo, Silvia Laura Bosello, Lucrezia Verardi, Enrica Fiori, Fabrizio Cocciolillo, Biagio Merlino, Angelo Zoli, *Maria Antonietta D'Agostino*
mariaantonietta.dagostino@unicatt.it

UOC di Reumatologia, Fondazione Policlinico Universitario A Gemelli IRCCS, Università Cattolica del Sacro Cuore, 00168 Roma, Italy (FL, PGC, SLB, LV, AZ, MAD); UOC di Pronto Soccorso e Medicina d'Urgenza, Presidio Ospedaliero Santo Spirito, Rome, Italy (EF); Nuclear Medicine Unit, Fondazione Policlinico Universitario A Gemelli, IRCCS, Rome, Italy (FC); Department of Radiological and Hematological Sciences, Section of Radiology, Fondazione Policlinico Universitario A Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy (BM)

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Adult-onset Still's disease after mRNA COVID-19 vaccine

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We report a case of severe adult-onset Still's disease (AOSD) presenting in a patient after receiving the mRNA-1273 COVID-19 vaccine (Moderna). A 45-year-old healthy woman developed a sore throat, intermittent headache, and fever of 38·3°C at 5 days after the second dose of the vaccine, approximately one month after the first dose. Over the next few days, she continued to have persistent daily fevers of up to 40°C despite consistent use of acetaminophen and nonsteroidal anti-inflammatory drugs. She subsequently developed severely debilitating myalgias, arthralgias, and pleurisy that ultimately prompted her to seek medical attention.

On admission to hospital, she had daily fevers of ≥39˚C and developed acute hypoxic respiratory failure requiring a 100% non-rebreather mask. Initial laboratory testing was notable for a leukocytosis, elevated erythrocyte sedimentation rate (85 mm/h; reference range 0–20 mm/h), C-reactive protein, and ferritin concentration (table). Cardiac biomarkers were increased, including troponin I to 0·35 ng/mL (reference range 0·00–0·04 ng/mL) and NT-proBNP to 1815 pg/mL (reference range 0–125 pg/mL). Imaging studies were notable for diffuse bilateral infiltrates on chest x-ray, no pulmonary embolus on chest CT scan, and left supraclavicular lymphadenopathy on neck CT and MRI.

	On admission, hospital day 1	On hospital transfer, hospital day 6	3 days after treatment initiation, hospital day 12	At follow-up (2 weeks of treatment)
Haemoglobin, ×10⁹ cells per L (reference range 11·2–15·7)	10·3	11·0	7·9	9·7
White blood cells, ×10⁹ cells per L (reference range 4·0–11·0)	22·1	29·9	24·5	21·4
Platelets, ×10³ cells per µL (reference range 150–400)	346	494	1088	649
Absolute neutrophil count, ×10³ cells per µL	19·6	26·5	..	17·1
Absolute lymphocyte count, ×10³ cells per µL	1·3	1·9	..	3·0
C-reactive protein, mg/dL (reference range 0·0–1·8)	27·7	277·8	154·8	2·1
Ferritin, ng/mL (reference range 8–252)	2911	14375	1523	160

Table: **Results from laboratory testing of patient at different timepoints**

The patient had an extensive infectious work-up that was negative, including repeated COVID-19 nasopharyngeal PCR testing. She was treated empirically with antibiotics for suspected community acquired pneumonia and her hypoxia resolved within 24 h. After 6 days in the hospital, she continued to have daily fevers of ≥39°C, debilitating arthralgias and myalgias, and increasing inflammatory markers (table), and she was transferred to a tertiary care facility for further evaluation.

Initial laboratory testing at the tertiary care facility showed persistent leukocytosis, thrombocytosis, and increasing C-reactive protein, ferritin, and liver enzyme concentrations. On the second day of admission she developed an evanescent salmon-coloured rash over the upper back, dorsal aspect of the hands, and bilateral thighs occurring with fevers. Serological testing including rheumatoid factor, cyclic citrullinated peptide antibody IgG, and antinuclear antibody was negative. After a thorough unremarkable infectious and malignancy work-up was completed, the patient was diagnosed with AOSD. At the time of diagnosis, according to the Yamaguchi classification criteria of AOSD, the patient met three of four major criteria (fever, typical rash, leukocytosis) and four of five minor criteria (sore throat, lymphadenopathy, abnormal liver function tests, and negative rheumatoid factor and antinuclear antibody).[1] The patient started treatment with prednisone 60 mg daily (1 mg/kg per day) with immediate resolution of her fevers and skin rash, and rapid improvement of her arthralgias and myalgias over the subsequent 3 days. There was a worsening thrombocytosis for the first few days after treatment initiation, which was deemed to be reactive and eventually improved with the rest of the inflammatory markers.

AOSD is a rare multisystem inflammatory disorder that mostly affects young adults (16–35 years).[2] The cause is unknown, and the diagnosis is based on a constellation of clinical criteria.[1] AOSD is often characterised by high spiking fevers, arthritis or arthralgias, and an evanescent salmon coloured rash on the trunk and extremities. Other associated features include sore throat, myalgias, lymphadenopathy, splenomegaly, and serositis. Laboratory findings consist of substantially elevated ferritin concentrations, leukocytosis with neutrophilic predominance, anaemia, and elevated acute phase reactants.[2] AOSD is typically a diagnosis of exclusion. The pathogenesis of AOSD is thought to involve aberrant activation of the innate immune system leading to cytokine storm with high concentrations of interleukin (IL)-1, IL-6, and IL-8.[2]

To our knowledge, this is the first reported case of AOSD after receiving an mRNA COVID-19 vaccine. However, we cannot exclude the possibility that the timing with regard to vaccination was coincidental. There have been two other published cases of AOSD presenting after COVID-19, but none after receiving a COVID-19 vaccine.[3,4] The onset of this patient's symptoms were 5 days following the second dose of the vaccine and persisted for nearly 2·5 weeks before initiation of treatment; this supports the idea that this represented a new onset AOSD rather than a hyper-inflammatory response to vaccination. The extensive work-up ruled out infectious and other inflammatory conditions that mimic AOSD. She currently remains asymptomatic 2 months after treatment was initiated with steroids and later anakinra; it will be difficult to tell whether this case will follow a monophasic or intermittent pattern of disease until treatment is weaned.

The mechanism by which COVID-19 infection or vaccination could trigger AOSD is unknown.[3,4]

There is abundant evidence that severe COVID-19 infection can induce a hyperinflammatory response through activation of the innate immune system and overproduction of proinflammatory cytokines (eg, IL-1, IL-6, IL-18, IFN-γ).[5] Similar to AOSD, IL-1 activation appears to play an important role in the immune activation of primary COVID-19, evidenced by the therapeutic efficacy of selective IL-1 inhibition in treatment of both disease processes.[2,6] It is suspected that mRNA vaccines might induce an immune response both by direct activation of the innate immune system through pattern recognition receptors such as toll-like receptors (TLRs) and RIG-I-like family receptors, and by activating the innate and adaptive immune response by the antigen made through transcription of the mRNA.[7] Studies have shown that the SARS-CoV-2 spike protein acts as a pathogen-associate molecular pattern, thereby inducing inflammation via TLR-mediated pathways leading to overproduction of cytokines and systemic inflammation.[8,9] Similar mechanisms of innate immune system activation by TLR signalling pathways, leading to cytokine overexpression and immune cell activation, are also implicated in the pathogenesis of AOSD, usually with either viruses or vaccines introducing pathogen-associate molecular pattern or damage-associated molecular patterns initiating the inflammatory cascade.[2]

Across the USA, over 200 million individuals have received at least one dose of mRNA COVID-19 vaccines without any serious adverse effects.[10]

We declare no competing interests. The patient provided consent for this Comment.

Daniel Magliulo, Soumya Narayan, Frances Ue, Afroditi Boulougoura, Fadi Badlissi
dmagliul@bidmc.harvard.edu

Beth Israel Deaconess Medical Center, Department of Rheumatology (DM, AB, FB), Cambridge Health Alliance, Cambridge Hospital (SN, FU), Harvard Medical School, Boston, MA 02215, USA

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