Letter to the Editor (Case report)

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SARS-CoV-2 multisystem inflammatory syndrome in an adult presenting with polyarthritis treated with anakinra**Rheumatology key message**

- Rheumatologists should consider COVID-19 MIS-A and AOSD/MAS when evaluating hyperinflammatory syndromes with multiorgan dysfunction.

DEAR EDITOR, Coronavirus disease 2019 (COVID-19) multi-system inflammatory syndrome in adults (MIS-A) is a new inflammatory disorder characterized by fever and cardiovascular, gastrointestinal, mucocutaneous and neurologic symptoms, with a striking absence of severe pulmonary illness, presenting either simultaneously or subsequently to a recent positive COVID-19 test [1]. This is likely the same as the better-described condition of multisystem inflammatory syndrome in children (MIS-C) [2]. Both of these are thought to be post-infectious complications. Pathophysiology remains unknown, but it is characterized by abnormal inflammatory markers, including CRP, ferritin and IL-6 [3].

We describe a case of COVID-19 MIS-A in a patient who responded to treatment with anakinra. This case is unique because the patient presented with inflammatory arthritis, which is rarely reported in COVID-19 MIS-A, and its presence enabled comparisons between adult-onset Still's disease (AOSD), and its complication, macrophage activation syndrome (MAS).

We encountered a 58-year-old male with medical history of hypertension, gout and mild severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on 1 April 2021, who presented on 1 May 2021 with malaise, fever and inflammatory arthritis of the left wrist, right ankle and left first MTP joint. Two weeks before hospitalization, he was prescribed ibuprofen and prednisone for presumed gout, without symptom resolution. He was febrile to 103°F, tachycardic and hypotensive, with leucocytosis, and elevated ESR, CRP, procalcitonin and ferritin. On examination, his left wrist was inflamed and tender to palpation and movement. He was started on antibiotics and admitted for presumed septic arthritis. However, culture of the left wrist SF did not reveal any organisms.

Within 72 h, he developed diarrhoea, nonexudative conjunctivitis, shock and respiratory distress, ultimately requiring intubation and vasopressor support. CT angiogram of the chest showed minimal ill-defined airspace opacities in the left lower lobe, and antibiotics were

broadened. Transthoracic echocardiogram revealed biventricular global systolic dysfunction. Norepinephrine, dopamine and vasopressin were started. He became anuric and continuous renal replacement therapy was started. He developed progressive laboratory abnormalities, with his ferritin level peaking at 25 622 ng/ml (reference range 30–400), leucocyte count at 55 000 K/μl (reference range 4.4–11.3), procalcitonin at 272 ng/ml, ESR >130 mm/h (reference range 0–25) and CRP at 32.8 mg/dl (reference range <0.5).

Extensive evaluation for bacterial, viral or fungal infection was negative. ANA and subserologies, RF, myositis panel and ANCA panel were negative. Flow cytometry for lymphoma/leukaemia, T and NK cell levels, and genetic screening for clonality were within normal limits. IL-2R alpha levels were elevated at 8595 U/ml (reference range 241–846).

COVID-19 MIS-A was considered, and on day 5, treatment was started with methylprednisolone 1 g i.v. daily for five days, and anakinra 100 mg every 48 h (dose adjusted for renal insufficiency). The patient had rapid clinical improvement on this combination therapy. In the following week, the patient was titrated off vasopressor support, extubated and transitioned to intermittent haemodialysis. Within 1 month, he made a full renal recovery. A repeat transthoracic echocardiogram also showed normal biventricular functioning. Laboratory abnormalities began to downtrend and eventually normalized. Anakinra and prednisone were gradually tapered. At last follow-up, he had ongoing memory impairment but no other persistent symptoms or organ dysfunction.

Table 1 [4, 5] compares the Yamaguchi criteria for AOSD and the Centers for Disease Control criteria for COVID-19 MIS-A. There was a question of AOSD with MAS given the initial presentation of fever and inflammatory arthritis, with subsequent hyperferritinemia and organ dysfunction. However, the patient lacked the classic rash, pharyngitis and lymphadenopathy of AOSD, so in the setting of recent COVID-19 infection and new multiorgan failure, we favoured MIS-A. Additionally, cardiac dysfunction without pericarditis or myocarditis is rare in AOSD/MAS but exceedingly common in COVID-19 MIS-A. Although AOSD/MAS and COVID-19 MIS-A are both marked by hyperinflammation and multiorgan dysfunction, other clinical features and a history of recent COVID-19 infection may be essential to differentiate between the diagnoses.

The unusual presenting symptom of inflammatory arthritis has not yet been described in the literature for COVID-19 MIS-A. Additionally, although most cases of MIS-A in the literature were treated with IVIG, glucocorticoids and tocilizumab, this case is unique for the successful use of anakinra for COVID-19 MIS-A. Rheumatologists should be aware of this condition, which can mimic other severe systemic diseases

TABLE 1 Criteria for diagnosis of AOSD and COVID-19 MIS-A

Yamaguchi criteria for AOSD	CDC criteria for COVID-19 MIS-A
<p>Major criteria:</p> <p>Fever $>39^{\circ}\text{C}$, lasting 1 week or longer</p> <p>Arthralgia or arthritis, lasting 2 weeks or longer</p> <p>Typical rash</p> <p>Leucocytosis $>10\,000\text{ K}/\mu\text{l}$ with $>80\%$ polymorphonuclear cells</p> <p>Sore throat</p> <p>Minor criteria:</p> <p>Recent development of significant lymphadenopathy</p> <p>Hepatomegaly or splenomegaly</p> <p>Abnormal liver function tests</p> <p>Negative tests for ANA and RF (IgM)</p> <p>Exclusion criteria:</p> <p>Infections</p> <p>Malignancies</p> <p>Other rheumatic diseases</p> <p>Five or more criteria are required with two or more being major criteria for diagnosis of AOSD</p>	<p>Clinical criteria:</p> <p>Subjective fever or documented fever $\geq 38^{\circ}\text{C}$ for $\geq 24\text{ h}$ prior to hospitalization or within the first 3 days of hospitalization, and at least three of the following clinical criteria occurring prior to hospitalization or within the first 3 days of hospitalization. At least one must be a primary clinical criterion.</p> <p>Primary clinical criteria:</p> <p>Severe cardiac illness</p> <p>Rash and non-purulent conjunctivitis</p> <p>Secondary clinical criteria:</p> <p>New-onset neurologic signs and symptoms</p> <p>Shock or hypotension not attributable to medical therapy</p> <p>Abdominal pain, vomiting or diarrhoea</p> <p>Thrombocytopenia</p> <p>Laboratory evidence:</p> <p>Elevated levels of at least two of the following: CRP, ferritin, IL-6, ESR, procalcitonin</p> <p>A positive SARS-CoV-2 test during the current illness by RT-PCR, serology or antigen detection</p>

Information obtained from [4, 5]. AOSD: adult-onset Still's disease; CDC: Centers for Disease Control; COVID-19: coronavirus disease 2019; MIS-A: multisystem inflammatory syndrome in adults; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

including AOSD, haemophagocytic lymphohistiocytosis/MAS, or even severe gout or septic arthritis.

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Data availability statement

Data derived from public domain resources, with information to access these resources provided in the references section.

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