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First manifestation of adult-onset Still's disease after COVID-19

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Adult-onset Still's disease (AOSD) is a rare inflammatory disorder that usually affects young adults, with a bimodal peak at ages 15–25 years and 36–46 years. The disease is characterised by fever of more than 39°C, transient skin rash, leucocytosis, arthralgia, arthritis, or a combination of these symptoms.[1] In addition to at least two of the aforementioned major criteria, the Yamaguchi criteria for the diagnosis of AOSD also require the presence of minor criteria—ie, sore throat, lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function tests, and negative tests for antinuclear antibodies and rheumatoid factor.[1] Infections, malignancies, and other rheumatic diseases need to be excluded. The cytokine interleukin (IL)-1 has a central role in the pathogenesis of AOSD; inhibition of the IL-1 pathway using monoclonal antibodies or IL-1 receptor antagonists significantly ameliorates the disease.[2] IL-1 drives an intense innate immune response by activating neutrophils, macrophages, and mast cells, and by promoting overexpression of several proinflammatory cytokines, including IL-6, IL-8, IL-17, IL-18, and TNF.[3] Viral or bacterial infections have been proposed as potential triggers, but the exact mechanisms underlying AOSD onset remain largely unknown.[4]

SARS-CoV-2 emerged in late 2019, causing the COVID-19 pandemic. AOSD and COVID-19 share several clinical and laboratory features, including systemic inflammation, unremitting fever, high serum ferritin, and a potentially life-threatening cytokine release syndrome. Data obtained from single-cell analysis revealed IL-1β-associated inflammasome signatures and a significant expansion of CD14-positive, IL-1β-positive monocytes in the peripheral blood of patients with severe COVID-19.[5,6] Thus, AOSD and the severe immune overreaction which occurs in some patients with COVID-19 might be triggered by the same mechanisms.

Here, we report a case of severe AOSD manifestations emerging in a patient suffering from long-term sequelae of COVID-19 for 6 months. In Germany, in March, 2020, a 29-year-old White woman with no notable medical history developed signs of SARS-CoV-2 infection including sore throat, headache, anosmia, ageusia, generalised weakness, shortness of breath, diarrhoea, and chilblain-like skin eruptions of the toes. The patient tested positive for SARS-CoV-2 by RT-PCR from a nasopharyngeal swab. There was no need for therapy or hospitalisation. RT-PCR tests for SARS-CoV-2 were negative on day 15 after the onset of first symptoms. The patient continued to have elevated temperatures of up to 38·0°C for another 8 days.

After 24 days, the patient seemed to have recovered from COVID-19, but 4 days later her temperature was elevated to 38·3°C, and she presented with transient maculopapular rashes lasting for up to 2 h in various locations, arthralgia, headache, sore throat, and increased sweating at night. On day 29 after first onset of symptoms, another oropharyngeal swab was taken and showed a positive test result for SARS-CoV-2. For detection of SARS-CoV-2-specific antibodies, five serum samples between April and May, 2020, were analysed by different commercial serological assays. The patient tested positive for antibodies against the nucleocapsid protein (Roche Diagnostics, Mannheim, Germany, and Abbott, Wiesbaden, Germany) but negative for IgM and IgG against spike protein (Euroimmun Diagnostik, Lübeck, Germany; Diasorin, Dietzenbach, Germany; and Immundiagnostik, Bensheim, Germany). IgA tested using the Euroimmun assay showed low to borderline values. All samples did not show neutralising activity by SARS-CoV-2 plaque reduction neutralisation test. Of 522 patients with COVID-19 tested for all aforementioned assays at the University Hospital Cologne (Cologne, Germany), only four other individuals shared the same constellation of positive antibody results. SARS-CoV-2-reactive memory CD4-positive T cells did not show signs of recent activation (Ki-67, CD38) on day 199 and displayed production of the cytokines TNF, IL-2, interferon-γ, IL-21 and IL-10, comparable to other patients with mild COVID-19.[7] During the entire 6-month period, the patient had persistent fatigue, resting tachycardia, shortness of breath, and recurrent macular rashes. A transthoracic echocardiogram did not show any abnormalities; nevertheless, the formerly athletic patient only managed to reach a workload of 100 W in exercise electrocardiogram.

In September, 2020, 6 months after the diagnosis of COVID-19, the patient noted a sore throat, but RT-PCR for SARS-CoV-2 was negative. In the days that followed, her general condition deteriorated because of myalgia, arthralgia, fever of up to 41·0°C, and lymphadenopathy. Laboratory tests showed an increased C-reactive protein (CRP) concentration of 49 mg/dL (reference value <0·5 mg/dL) and leucocytosis of $21{\cdot}39 \times 10^9$ cells per L (reference range $4{\cdot}4–11{\cdot}3 \times 10^9$ cells per L). In addition, liver enzymes were elevated, with an AST value of 123 U/L and an ALT value of 165 U/L (reference value <35 U/L). Moreover, NT-pro-BNP was significantly increased to 3856 pg/mL (reference value <125 pg/mL) and troponin T to 463 pg/mL (reference value <100 pg/mL). Finally, systemic inflammation was confirmed by an erythrocyte sedimentation rate of up to 94 mm/h (reference range <25 mm/h), ferritin values of up to 1771·8 ng/mL (reference range 15–150 ng/mL), and IL-6 serum concentrations of up to 865·0 pg/mL (<8 pg/mL). Laboratory tests for antinuclear antibodies, rheumatoid factor, and diverse infectious agents were negative.

Due to recurrent NSAID-refractory fever episodes with up to 41°C over a period of 3 days, the patient was admitted to hospital. Other clinical symptoms included concomitant evanescent salmon-coloured rashes, episodes of hypotension, and resting tachycardia. Mild pericarditis with a small amount of pericardial effusion and pleural effusions were detected by cardiac MRI. 3 days after admission to hospital, the patient was transferred to an intermediate care unit because of respiratory distress. A chest x-ray revealed pulmonary infiltrates. Vasculitis was ruled out by PET-CT; however, a bilateral basal pneumonia with partly encapsulated pleural effusions was detected. Bronchoscopy with bronchoalveolar lavage revealed an acute bronchitis with distinct collapse phenomena and mild non-purulent secretion. Analysis of peripheral blood samples did not show any viral or bacterial pathogens.

Since an infectious disease or malignancy could be ruled out, AOSD was diagnosed. At this time point, the patient fulfilled all major and minor criteria of the Yamaguchi classification.[1] Treatment with intravenous prednisolone at 50 mg/day was introduced, but did not lead to sufficient improvement resulting in an increase of prednisolone dosage to 100 mg 3 days later. Although the CRP value declined, the clinical situation did not show adequate improvement and deteriorated a few days later, with extension of pericardial effusion to 1·4 cm pancordially within 24 h and transthoracic echocardiogram showing beginning congestion of the vena cava. Moreover, a swinging heart phenomenon and breath-dependent drops of pulse and systolic blood pressure below 60 mmHg were observed. On that day, the patient was transferred to the University Hospital Cologne because of her poor condition. At the hospital, an additional treatment with the IL-1 receptor antagonist anakinra (subcutaneously at 100 mg/day) was initiated, and led to a significant improvement of clinical symptoms. The pericardial effusion resolved within 24 h. The patient was released from hospital 5 days later. 4 weeks later, all laboratory values had returned to normal. Prednisolone was slowly tapered, while treatment with anakinra was maintained during the following months.

To the best of our knowledge, this is the first report of AOSD onset after COVID19. The case of this patient shows that long COVID can mimic AOSD and delay diagnosis. This finding is important, because the number of patients with long-term sequelae of COVID-19 is continuously rising and early treatment of AOSD might prevent complications and reduce mortality. In this patient, the initial symptoms of COVID-19 were similar to those of AOSD. However, temperature was only slightly elevated during SARS-CoV-2 infection, indicating that AOSD was not present at this time, because AOSD is defined by intermittent fever above 39°C for at least 1 week. Remarkably, COVID-19 and AOSD share not only clinical features, but also common pathogenic pathways. In particular, IL-1 seems to have a central role in both diseases. Targeting IL-1 is a highly efficient treatment for AOSD, and growing evidence points towards a similar role for IL-1 in COVID-19 hyperinflammation. A recent study[8] has shown that treatment with anakinra significantly reduced hyperinflammation, respiratory insufficiency, and mortality in patients admitted to hospital with severe COVID-19. By contrast, IL-6 receptor inhibition was less efficient and reduced mortality only in a subset of patients.[8] These findings are in line with previous observations showing that treatment with anakinra was associated with clinical improvement in patients with COVID-19-associated acute respiratory distress syndrome.[9] These clinical observations support the assumption that IL-1 has a critical role in

hyperinflammation during severe COVID-19. Interestingly, our patient had similar symptoms during SARS-CoV-2 infection and AOSD onset. These symptoms included dyspnoea, which is generally rare in AOSD affecting only approximately 5% of patients.[10] The common role of IL-1 in the pathogenesis of AOSD and COVID-19 could explain the close similarities between both diseases. We postulate that a potentially misdirected immune response against SARS-CoV-2 could have triggered disease onset of AOSD in our patient.

We declare no competing interests. The patient provided informed consent for publication of this Comment. UW and DMK contributed equally.

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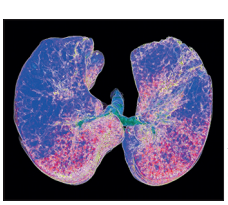
Rational repurposing of tocilizumab for treatment of lung fibrosis in systemic sclerosis

Recent approval of the anti-interleukin (IL)-6 receptor antibody tocilizumab by the US Food and Drug Administration (FDA) for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease is a welcome step towards better treatment and outcomes for systemic sclerosis. Systemic sclerosis-associated interstitial lung disease has emerged as one of the major causes of death in a disease with very high burden and unmet need. Tocilizumab is the second drug approved by the FDA for this indication and the first biological agent approved for any aspect of systemic sclerosis,[1] underpinned by a substantial body of translational medical research.

That FDA approval was based on two clinical trials that did not meet their primary efficacy endpoint of significant benefit according to the modified Rodnan skin score (mRSS) is perhaps a surprise. This is a reflection of the robustness of the data for the lung fibrosis subgroup in the phase 3 focuSSced trial[2] and the limitations of using the mRSS as a clinical trial endpoint. Skin and lung fibrosis are not the same in early systemic sclerosis, and the tendency for mRSS to improve at a group level even in patients on placebo makes it a challenging outcome measure. Conversely, lung function decline appears to be a consistent feature of systemic sclerosis, and reduction in the rate of decline has been shown for nintedanib[3] and tocilizumab. These results could have broader implications for future clinical trial design in systemic sclerosis. It is notable that there was benefit in a range of other endpoints, including the American College of Rheumatology composite combined response index in systemic sclerosis, suggesting further potential effects on systemic sclerosis.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It is not a surprise that blocking IL-6 signalling is beneficial in patients with systemic sclerosis-associated interstitial lung disease in view of compelling data