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Case Report

Severe Covid-19 is a Risk Factor for Gout Even in Hypouricaemic ICU Patients. Sign of Arousal of NLRP3 Activation?

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Received: May 14, 2021; **Published:** June 08, 2021

Abstract

Severe Acute Respiratory Syndrome Corona Virus type 2 (SARS-CoV2) causes a mild to a fulminant respiratory viral infection by entering via ACE2 receptors. In some cases, the host response is upregulated to a fulminant cytokine storm or better cytokine release syndrome (CRS). In early infections with a mild course, it has been shown that increased levels of interleukin 1 beta, interleukin 1 Receptor Antagonist, interleukin 6, tumor necrosis factor alpha, interleukin 10 and soluble urokinase plasminogen activator receptor are in circulation with an increased expression of NOD-Like Receptor Pyrin domain 3 (NLRP3) [1]. Some studies indeed have shown a prompt clinical improvement with IL1 blockade [2-5]. At Intensive Care Units these SARS-CoV2-induced cases are often seen with an acute respiratory distress syndrome (ARDS) being the predominant and primary cause of death among SARS-CoV2 infected ICU patients but the pathobiological mechanism is still under debate. Here two cases are described with an acute crystal-proven gout during admission on our ICU department for COVID-19 while on hypercaloric feeding, having a low serum rate, but clearly no history of previous gout.

Keywords: *Acute Respiratory Distress Syndrome; Arthritis; COVID-19; Gout*

Introduction

Severe Acute Respiratory Syndrome Corona Virus type 2 (SARS-CoV2) causes a mild to a fulminant respiratory viral infection by entering via ACE2 receptors. In some cases, the host response is upregulated to a fulminant cytokine storm or better cytokine release syndrome (CRS). In early infections with a mild course, it has been shown that increased levels of interleukin 1 beta, interleukin 1 Receptor Antagonist, interleukin 6, tumor necrosis factor alpha, interleukin 10 and soluble urokinase plasminogen activator receptor are in circulation with an increased expression of NOD-Like Receptor Pyrin domain 3 (NLRP3) [1]. Some studies indeed have shown a prompt clinical improvement with IL1 blockade [2-5]. At Intensive Care Units these SARS-CoV2-induced cases are often seen with an acute respiratory distress syndrome (ARDS) being the predominant and primary cause of death among SARS-CoV2 infected ICU patients but the pathobiological mechanism is still under debate.

Macrophages are key sentinel cells in the respiratory system; following a viral infection with SARS-CoV2 these macrophages hardly induce beta-interferon, but these do get to induce chemokines such as CXCL10/IFN-gamma-inducible protein 10 and interleukin 1 via the NLRP3-inflammosome. This hyperactivation of the inflammasome on a locoregional level is also seen in acute gouty attacks, well-known to affect obese patients with a so-called metabolic syndrome. These gouty attacks can be inhibited both by NLRP3 inhibition as well as interleukin 1 receptor antagonist injection therapy [6,7].

Obesity has been widely reported to be associated with disease progression of coronavirus disease a so-called COVID-19. A pre-existing cardiovascular disease seems to be linked with inflammation as an important driver in COVID-19. In addition, risk factors such as diabetes, pulmonary disease or immunosuppressive conditions are causally linked to worse outcome following the often hyperinflam-

matory response during severe corona disease. It is recently suggested that gout patients are an under-recognized group at high risk of COVID-19 [8].

We present two recent cases of ICU patients who never had gout attacks in history, but had risk factors for cardiovascular disease and who were diagnosed with SARS-CoV2 infection and a subsequently developed ARDS during which they experienced a debute of an acute crystal-proven gout attack while circulating serum urate concentrations were low. These cases are of importance to orthopedic surgeons, ICU specialists and rheumatologists obviously. Is there a rationale for these gout attacks?

Case Report

A 76 year old male was admitted to the intensive care with the diagnosis of acute respiratory disstress syndrome (ARDS) due to COVID-19. Two days prior to the ICU admission he was referred to the department of pulmonology. The patient had a positive oro-nasopharyngeal swab sample test for SARS-CoV2 resulting into the diagnosis of COVID-19 and because of hypoxia he was treated with supplemental oxygen. His medication included remdesivir and systemic corticosteroids according to local guideliness. The previous history included obesity (BMI 30.5), hypertension, peripheral vascular disease and COPD.

On ICU admission the patient was immediately intubated and mechanically ventilated in prone position. The patient had multiple sepsis episodes caused by *Streptococcus pneumoniae, Pseudomonas* and *Enterococcus faecalis*. He was also treated for pulmonary Aspergillosis and a stomatits caused by herpes simplex. Target quantity of protein was reached by continuous enteral nutrition with a protein--rich formula.

On ICU day 35 he developed a fulminant gouty arthrtitis of the left knee and leftsided MetaTarsal Phalangeal joint 1 (MTP1 = podagra). MSU crystals were present in the aspirated joint fluid as demonstrated with polarized light microscopy, see figure 1. He received 100 mg subcutaneously Anakinra once daily during 5 days cf registration in the Netherlands (Table 1). Clinical signs and symptoms disappeared within 4 days. Laboratory results showed a decline in CRP (Table 2). We also noticed an uneventful recovery from severe COVID-19 with a prompt decline in disease severity, lower FiO_2 fractions and PaO_2/FiO_2 ratio. On ICU day 32 a tracheostomy was performed which was removed at ICU day 39. The patient was discharged on ICU day 40.

Patient 1								
	Before	**D1 Anakinra**	**D2 Anakinra**	**D3 Anakinra**	**D4 Anakinra**	**D5 Anakinra**	**D6**	**D7**
CRP(< 5 mg/dl) Urate (mM/L)		125	149 0.17	104 0.17	56 0.18	37 0.22	20 0.25	13 0.25
eGFR Screat mmol/l		> 90 59	> 90 52	> 90 47	> 90 50	> 90 53	> 90 48	> 90 46
Urine Urate mol/24hr FeUA (%)				 6.00 5.5	 6.60 5.1		 6.00 3.4	 4.1 2.2

Table 1: *Data during the 5 days where the patient was treated because of crystal proven gout in MTP1 of the left foot and knee. Gout was diagnosed at ICU day 35. The fractional urate excretion (FeUA) is commonly 7.0 - 8.0% in normal non-gout patients but in gout on average 4.5%: lower as these are often underexcretors and this patient the excretion range was 5.5% to 2.2%.*

Patient 2										
	Before	**D1 Anakina**	**D2 Anakinra**	**D3 Anakinra**	**D4 Anakinra**	**D5 Anakinra**	**D6 Anakinra**	**D7**	**D8**	**D9**
CRP(< 5 mg/dl) Urate (mM/L)		425	195	101	61	37 0.16	33 0.15	37 0.13	52 0.13	59
eGFR Screat mmol/l		> 90 52	> 90 57	> 90 61	> 90 52	> 90 48	> 90 44	> 90 40	> 90 40	> 90 41
Urine Urate mol/24hr FeUA (%)							5.55 4.5	6.0 4.2		

Table 2: *Data during the 5 days where the patient was treated because of crystal proven gout in MTP1 of the left foot after COVID-19 at ICU day 18. The fractional urate excretion (FeUA) is commonly 7.0-8.0% but in gout lower and here about 4.5% which is an average value in gout patients.*

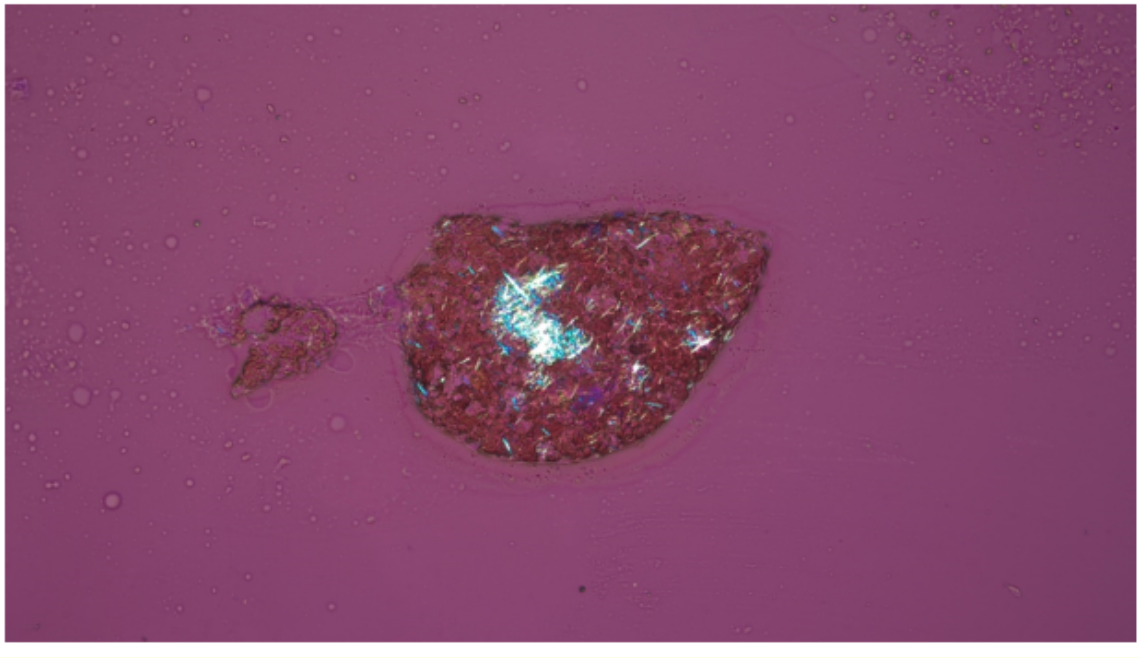

Figure 1: *Polarized light microscopy of knee puncture with mild gonarthritis of patient one.*

A 72 year old male patient without significant past diseases with the diagnosis of acute respiratory disstress syndrome (ARDS) due to COVID-19 requiring mechanical ventilation at the ICU. BMI on admission was 29. Initially the patient was treated with high flow nasal cannula.

At ICU day 3 he was intubated due acute hypoxemic respiratory failure due to COVID-19. The patient showed a progression of OVID-19 disease to severe disease and critical illness and also developed ICU acquired pneumonia and several episodes of sepsis with positive sputum and blood cultures for *Staphyloccus areus, Streptococcus faecium* and *Klebsiella pneumoniae*. The patient had nasogastric tube feeding with high energy and protein intake.

On ICU day 19 the patient developed a painful arthritis caused by MSU crystal-proven gout of the leftsided MTP1. Treatment with Anakinra 100mg subcutaneously during a 5 day period was effective in controlling the manifestations of gout as well as of the severity of COVID-19.

Due to prolonged mechanical ventilation due to critical illness polyneuropathy and myopathy the patient received a tracheostoma tube from ICU day 48 - 53. The patient's clinical status gradually improved and on ICU day 63 he was discharged to the general ward.

Discussion and Conclusion

Commonly ICU departments rarely encounter patients with acute gout. Most commonly this type of arthritis is suspected in the context of hyperuricemia, but it is well known that in the case of an acute attack the serum urate level can be within normal range [9]. There is a possibility that COVID-19 patients may develop an acute gout attack in specific patient groups prone to urate accumulation due to lower fractional urate excretions particularly in the setting of an activated cytokine response as such an attack is an interleukin 1 driven inflammatory disease. Our case reports demonstrate that crystal-proven gouty arthritis can present even when serum urate concentrations are low i.e. below the saturation level in the blood compartment and interestingly these patients were lacking a gout history prior to these attacks though obviously were low excretors regarding urate which is biologically explained by the presence of specific urate transporters.

COVID-19 is a serious hyperinflammatory disorder in about 20% of those who contract SARS-CoV2. Our results imply that patients with COVID-19 disease may be at greater risk for developing gouty arthritis possibly due to the activated NLRP3-inflammasome - interleukin 1 system. We here show that even at a low serum urate a gouty arthritis may develop during a katabolic state where the compartments of the peripheral joints may be susceptible to 1) acute monosodium urate deposition in more acidic microenvironments as may develop during katabolism and 2) systemic arousal of the NLRP3 inflammasome as this is associated with COVID-19. There are many studies trying to explain the lower levels of SUA during an acute gout attack. Knowing that uric acid is an antioxidant, it may be consumed in a free radical reaction during an episode of systemic inflammation [10]. Additionally, dietary factors such as a hypercaloric and protein enriched enteral and parenteral feeding. Specific for ICU treatments in katabolic patients might have influenced this urate accumulation in specific joints resulting in gouty inflammation as well. These purine enriched dietary factors also explain why gout and not other crystal-associated diseases such as calcium pyrophosphates (CPP) would be presenting in these populations as these CPP would potentially also become manifest in elderly at ICU departments with a state of NLRP3 -inflammasome arousal. Although preliminary data, do not suggest that patients with inflammatory arthritis are at increased risk of COVID-19 our findings are consistent with previous statements suggesting that local inflammatory syndromes with a role for interleukin 1 as is supposed in COVID-19 may drive the disease process. Once crystals such as monosodium urate needles are deposited within the peripheral, often colder joints a prompt escalation of local inflammation may occur in a state with arousal of the NLRP3 inflammasome.

We speculate that regarding the inflammation of gouty arthritis in our patients also the role of neutrophils needs to be considered. Neutrophils provide a source of ATP and proteinase-3, which can process the IL1-β precursor into an active cytokine. In susceptible patients with risk factors for gouty attack such as obesity MSU is the priming agent by inducing gene expression for IL-1β and we hypothesize that gene expression by SARS-CoV-2 infection for Il-1β provides a uniquely clinically relevant translational signal and contributes to the hyperinflammatory micro-environment during flares of gouty arthritis. Taken together, our results indicate that gout should be considered as a potential COVID-19 sequel.

Clinicians who meet a peripheral monoarthritis, should always make a differential diagnosis with crystal-induced arthritides. Such patients with low serum urate levels and lack of gout history will not easily be classified when the ACR-EULAR criteria set is applied [12]. Clearly a puncture of affected joint then is mandatory to ascertain the diagnosis [13]. Orthopedics consulting an ICU should therefore be cautious when arthritis is encountered in these COVID-19 patients to misinterpret bacterial and MSU-induced arthritis.

An acute severe arthritic attack is an uncommon but serious complication in ICU patients in whom one has to consider a bacterial arthritis during ARDS secondary to severe COVID-19. The importance of recognizing gout is clear when considering therapeutic implications, as this gouty arthritis may well benefit from therapies that block interleukin 1 such as the interleukin 1 Receptor Antagonist Anakinra (short half-life) or possibly the for gout registered interleukin 1 monoclonal antibody Canakinumab (long half-life). The shorter half-life of Anakinra, also registered in the Netherlands for the use of complex gout [6] clearly is to be preferred on an ICU where changes to the worse may occur even every day or every hour or even every minute.

Anakinra is an interleukin 1 (IL1) Receptor Antagonist whereas Canakinumab is a monoclonal against IL1. IL1 inhibitor has a special interest in COVID-19 as reduced mortality is reported with a hazard ratio 0.45 [95% CI: 0.20 - 0.99] in Anakinra i.e. interleukin 1 blockade versus only 0.90 [95% CI: 0.41 - 1.96] in Tocilizumab/Sarilumab i.e. interleukin 6 blockade [11]. Though one should be cautious with the higher doses, as the early use of only intermediate doses of Anakinra in patients with moderate hyperinflation due to severe COVID-19 pneumonia is supposed to control hyperinflammation, with a better safety profile than the higher doses [12]. It is of course unclear whether the lower doses of Anakinra 100 mg SC QD we commonly use in acute gout still have efficacy regarding a better outcome in COVID-19.

Current treatment options to control inflammatory pain of acute gout in non-ICU-admitted patients include nonsteroidal anti-inflammatory drugs, colchicine and corticosteroids. Because interleukin 1 (IL-1β), a proinflammatory cytokine, plays a major role in mediating gouty inflammation we considered treatment of an interleukin 1 blocker [1-6]. Anakinra was very effective and the preferred treatment in our 2 patients, as it is an IL-1 Receptor Antagonist that inhibits the activity of both IL-1α and IL-1β. In the Netherlands Anakinra is registered for complex gout based on recent data [6] but its efficacy has not been demonstrated previously in patients with simultaneous COVID-19.

Our case reports contribute to the understanding of the inflammatory response during gouty arthritis in cases even with low serum urate; they contribute to the understanding of purine-rich hypercaloric feeding in katabolic states associated with COVID-19 in patients with a lower fractional urate excretion; they demonstrate one should be vigilant for acute gout on ICUs with fulminant arthritides as these specific patient groups could well benefit from therapies interfering with interleukin 1 signaling, such as Anakinra, a recombinant IL-1RA, that appears to be a double-edged sword.

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Volume 12 Issue 7 July 2021