Systemic inflammatory response and fast recovery in a pediatric patient with COVID-19

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Running title

Severe course of pediatric COVID-19

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Conflict of interest statement

The authors have declared that no conflict of interest exists.

Ethical approval

This study was carried out in accordance with the recommendations of the Ethical Committee of the second Faculty of Medicine, Charles University in Prague and University Hospital in Motol, Czech Republic. The protocol was approved by the Ethical Committee. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

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Main text

To the Editor:

The recently emerged SARS-CoV-2 virus causes pneumonia and, in severe cases, acute respiratory distress syndrome (ARDS) in adults, but its clinical picture can be markedly different in children, most of whom undergo only a mild or even asymptomatic course of the disease[1–3]. In some cases, however, profound systemic inflammatory response is triggered, sharing few similarities with the more commonly seen self-limited respiratory infection.

Here we report a case of an 8-year-old girl who manifested with fever (>40°C), headache, abdominal pain and vomiting, but no signs of respiratory involvement with only mildly elevated C-reactive protein (CRP, 27 mg/l, Fig 1A). Over the next 2 days she developed diffuse itchy maculo-papular rash (Fig 1B) and watery diarrhea with CRP of 139 mg/l. At this point, SARS-CoV-2 nasopharyngeal swab polymerase chain reaction (PCR) was negative. The girl was started on amoxicillin/clavulanic acid. However, her condition deteriorated with ongoing high-grade fever, diarrhea and headache necessitating hospital admission on day 5 from symptom

onset. She was febrile and dehydrated with severe abdominal pain, diarrhea and positive meningeal signs. She had high inflammatory parameters (CRP 267 mg/l, procalcitonin 70 µg/l), elevated D-dimers and urea, creatinine, liver enzymes, troponin and proNT-BNP. Stool PCR showed only weak positivity for rotavirus and astrovirus, chest X-ray was largely normal (Fig 1C), spinal tap suggested mild serous meningoencephalitis. At this point, the nasopharyngeal swab PCR was still negative, however, anti-SARS-CoV-2 IgG antibodies were positive, with negative IgM. Due to recurrent episodes of hypotension and other signs of septic shock the patient was started on intravenous ceftriaxone and transferred to an intensive care unit. Abdominal ultrasound suggestive of paralytic ileus with appendicitis and overall worsening of clinical status resulted in an empirical exchange of ceftriaxone for piperacillin, tazobactam and metronidazole and abdominal surgery on day 6 of the disease, which revealed serous peritonitis but no appendicitis or other pathology. Subsequent serology showed positive IgA against *Yersinia enterocolica,* but negative rectal swab culture.

After extubation and discontinuation of analgosedation on day 7, the patient's consciousness deteriorated towards Glasgow coma scale (GCS) of 7-8 on day 8, despite normal central nervous system magnetic resonance imaging (MRI) and lack of topical neurological symptoms. Here the patient developed dry cough for the first time. Even though all tests including the cerebro-spinal fluid, blood culture, urine, stool and broncho-alveolar lavage were negative for any microbial pathogens, with the sole exception of nasopharyngeal swab PCR positivity for SARS-CoV-2, her CRP and procalcitonin remained very high (199 mg/l and 28,4 µg/l respectively). The persistent elevation of inflammatory markers along with very high soluble IL-2 receptor (6326 IU/ml), ferritin (577 µg/l) and history of juvenile idiopathic arthritis (oligoarticular subtype, currently inactive without therapy) lead to suspicion of viral-induced macrophage activation syndrome (MAS) / secondary hemophagocytic lymphohistiocytosis (HLH), which however was not abundant in bone marrow aspirate and the patient did not fulfill diagnostic criteria for MAS/HLH[4]. Heart ultrasonography was repeatedly normal, making the diagnosis of Kawasaki disease unlikely. The patient was administered intravenous methylprednisolone (2mg/kg/day in 3 doses), one dose of 400 mg/kg intravenous immunoglobulins, prophylactic nadroparin and the piperacillin and tazobactam were discontinued due to apparent lack of effect in favour of ceftriaxone. This therapy lead to gradual improvement of clinical symptoms with full recovery of her consciousness by day 11. Her inflammatory markers, cardiac enzymes, liver and renal functions normalized apart from the mild hepatopathy most likely related to the combined antibiotic therapy. The patient was finally discharged from the hospital in good health on the 15^{th} day after onset of symptoms.

We observed a spike in markers of inflammation around day 8, coincident with the worsening of patient's symptoms. Of particular interest in the context of COVID-19 was the elevation of CRP and PCT, but relatively "low" levels of serum IL-6 (cytokine associated with severe course of the disease and higher mortality in adults[5]) – the patient reached IL-6 of 215 pg/ml (normal range 0-6 pg/ml) at the time of worst clinical symptoms. For comparison, adult patients admitted to our hospital with severe course of COVID-19 who required mechanical ventilation frequently reached IL-6 levels in the thousands. Soluble IL-2 receptor which is produced by activated mononuclear cells[6] was very high, while both monocytes and lymphocytes were normal on day 8 and increased only slightly between days 10 and 15 (Fig 2A). On the other hand, neutrophils and eosinophils peaked on day 8 and decreased sharply thereafter. While the elevation of neutrophils and lymphopenia are both well-established as negative prognostic markers of COVID-19 in adults[7], the role of eosinophils remains more elusive, with some reports suggesting they are decreased in severe cases[8]. Aside from the waxing and waning of leukocyte subpopulations, the pivotal role of innate immunity in defense against SARS-CoV-2 is further supported by the depletion and gradual recovery of complement (C3 and C4 proteins) during the disease (Fig 2B).

We additionally show stark changes in neutrophil phenotype during the course of the disease (Fig 2C). The expression of HLA-DR, previously described to be decreased in COVID-19[9], was low on day 8 and gradually recovered to normal levels. CD10, a marker of neutrophil maturation associated with immunosuppressive function[10], was markedly decreased during the worst clinical symptoms, suggesting efflux of young, active neutrophils from the bone marrow, but together with the inhibitory molecule PD-1L and CD15, a marker of activation in mature neutrophils, reached supra-normal expression during recovery as these cells matured. The adhesion molecule CD62L was low during the time of most fulminant infection, but its expression

recovered and was even elevated on day 19 at recovery. Together, these data suggest full activation and engagement of neutrophils during the disease with compensatory contraction of the response and contra-regulation of neutrophil phenotype during recovery.

In summary, our patient developed systemic inflammatory response to SARS-CoV-2 infection in absence of other infectious pathogens, which had some but not all hallmarks of secondary MAS/HLH and which quickly deteriorated and then resolved with corticosteroids, preventive anticoagulation and supportive therapy only. This case report illustrates the variability of clinical presentation of SARS-CoV-2 infection in children, which should be suspected in case of unexplained inflammatory symptoms even in the absence of signs of respiratory infection. Immunosuppressive therapy may be helpful for these patients.

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Impact statement

SARS-CoV-2 infection in children may trigger systemic inflammatory response without symptoms traditionally associated with COVID-19 in adults. Its course is characterized by the activation of the innate immune response and may resolve quickly with supportive therapy and intravenous corticosteroids.

References

1. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding.*Nat Med* . 2020. doi:10.1038/s41591-020-0817-4

2. Brough HA, Kalayci O, Sediva A, et al. Managing childhood allergies and immunodeficiencies during respiratory virus epidemics – the 2020 COVID-19 pandemic. *Pediatr Allergy Immunol* . 2020:0-3. doi:10.1111/pai.13262

3. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med* . 2020;382(17):1663-1665. doi:10.1056/NEJMc2005073

4. Henderson LA, Cron RQ. Macrophage Activation Syndrome and Secondary Hemophagocytic Lymphohistiocytosis in Childhood Inflammatory Disorders: Diagnosis and Management. *Pediatr Drugs* . 2020;22(1):29-44. doi:10.1007/s40272-019-00367-1

5. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID - 19 based on an analysis of data of 150 patients from Wuhan , China. *Intensive Care Med* . 2020. doi:10.1007/s00134-020-05991-x

6. Nelson DL, Rubin LA, Kurman CC, Fritz ME, Boutin B. An analysis of the cellular requirements for the production of soluble interleukin-2 receptors in vitro. *J Clin Immunol* . 1986;6(2):114-120. doi:10.1007/BF00918743

7. Zhang B, Zhou X, Zhu C, et al. Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19. *medRxiv* . 2020:2020.03.12.20035048. doi:10.1101/2020.03.12.20035048

8. Qin C, Zhou L, Hu Z, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* . 2020;2019(Xx Xxxx):4-10. doi:10.1093/cid/ciaa248

9. Wilk AJ, Rustagi A, Zhao NQ, et al. A single-cell atlas of the peripheral immune response to severe COVID-19. *medRxiv* . 2020. doi:https://doi.org/10.1101/2020.04.17.20069930

10. Marini O, Costa S, Bevilacqua D, et al. Mature CD10+ and immature CD10- neutrophils present in G-CSF–treated donors display opposite effects on T cells. *Blood* . 2017;129(10):1343-1356. doi:10.1182/blood-2016-04-713206

Figure legends

Fig 1

Blood biochemistry and markers of inflammation over the course of the disease (A). Exanthema on day 12 (B). Chest X-ray on day 6 (C).

Fig 2

Leukocyte subpopulations over the course of the disease (A). Complement protein C3 and C4 levels over the course of the disease (B). Neutrophil phenotype on day 8 (fulminant disease), 12 and 19 (recovery) in comparison to a healthy control (C).