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LETTER TO THE EDITOR

SARS-CoV-2 infection in a 7-year-old girl with pancytopenia during acute lymphocytic leukemia maintenance therapy

To the Editor:

Emerging in China in December 2019[1] and classified by the World Health Organization as causing pandemic disease in March 2020,[2] severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a major challenge in most nations. Austria, especially the region of Tyrol, is no exception. Currently, within a Tyrolean pediatric population of ≈132 000 aged <18 years,[3] 63 (0.05%) have had SARS-CoV-2 detected by PCR. Only two have been admitted to our pediatric department. In general, COVID-19 in children is rare, specifically in those aged <10 years, and its course appears milder than in adults.[4-6] However, some severe and even fatal cases in children have been reported.[7,8] Systemic immunosuppression renders adult patients with cancer more susceptible to infection,[9] possibly conferring an adverse prognosis in COVID-19.

Due to lack of literature, reassurance that SARS-CoV-2 infection per se is not life threatening to the most vulnerable children with aggressive cancer therapy is of immediate general interest. Hence, we report the case of a 7-year-old female patient with proven SARS-CoV-2 infection during maintenance therapy of acute lymphocytic leukemia (ALL).

ALL, diagnosed at age 6 years in October 2018, was treated according to the AIEOP-BFM 2009 protocol,[10] with reinduction completed in May 2019. Since then the child has received maintenance therapy (daily 6-mercaptopurine, weekly methotrexate). In December 2019, fever during bone marrow suppression prompted hospital admission, with discharge early in January 2020. Maintenance therapy was continued in a reduced dosage and gradually increased (target dosage, methotrexate 20 mg/m^2 by mouth once weekly, and 6-mercaptopurine 50 mg/m^2 by mouth once daily).

In mid-March, leukopenia, 1.5 G/L, and thrombocytopenia, 50 000 G/L, prompted a reduction in maintenance therapy. Three days later, COVID-19 was diagnosed in the patient's mother and the patient was reportedly febrile at night. Maintenance therapy was immediately suspended; as the patient's general health was good, she remained at home. Another 3 days later (day 4 of illness), high nonremitting fever with malaise prompted the child's hospital admission to a special isolation ward.

On evaluation, the patient's vital signs were unremarkable (heart rate 100 bpm, blood pressure 100/67 mm Hg, eupnea, temperature 36.0°C). On room air, oxygen saturation was 100%. Mild rhinitis was evident; her skin was pale, without petechiae or purpura, although small hematomata were present. Pneumonia was not clinically suspected, and roentgenograms were not obtained. Pancytopenia was present (leukocytes 0.8 G/L with neutrophils 0.5 G/L and lymphocytes 0.22 G/L, thrombocytes 5 G/L, hemoglobin 102 g/L); C-reactive protein (CRP) and interleukin-6 values were elevated at 21.7 mg/L and 20.6 ng/L, respectively. A blood culture yielded no growth.

SARS-CoV-2 genomic sequences were detected in a nasopharyngeal sample by PCR testing. Cefuroxime, begun on admission, was replaced the same day by meropenem (60 mg/kg/day in three doses) and gentamicin (5 mg/kg/day in one dose). Thrombocyte concentrates were transfused (15 mL/kg). Small blisters developed on the tongue, and acyclovir was begun (30 mg/kg/day in three doses; day 1). Lassitude worsened (day 5), with upward fluctuation in CRP values, and vancomycin was begun (40 mg/kg/day in two doses), with thereafter a fall in CRP and rise in leukocyte numbers (Figure 1).

Fever resolved (Figure S1) and gentamicin and acyclovir were terminated (day 7), as was vancomycin (day 8). SARS-CoV-2 RNA sequences were no longer detectable in the nasopharyngeal sample on day 9 (day 13 of illness). Laboratory findings on day 10 demonstrated improvement of blood counts (leukocytes 1.4 G/L, thrombocytes 63 G/L, and hemoglobin 91 g/L, with CRP 4.9 mg/L). On day 10, as the patient had been without signs or symptoms of COVID-19 for 4 days, meropenem was stopped and she was discharged home in good general condition. ALL maintenance therapy was resumed one week after discharge.

Of interest is that both parents worked in Tyrolean "hot spots" for COVID-19. The patient's brother was mildly ill when COVID-19 was diagnosed in the mother; he was not tested. The father was tested twice, without infection found.

Our experience with this patient—so far as we know, the first child with COVID-19 during pancytopenia induced by maintenance therapy for ALL—suggests reassuringly that the course of COVID-19 in pediatric patients can be mild even if assessed risk for complications is high, as with immunosuppression and pancytopenia. Our patient had only mild rhinitis with remitting fever and lingual blisters. Antibiotic and antiviral therapy was associated with swift improvement. Most importantly, her pulmonary status was clinically stable throughout her illness.

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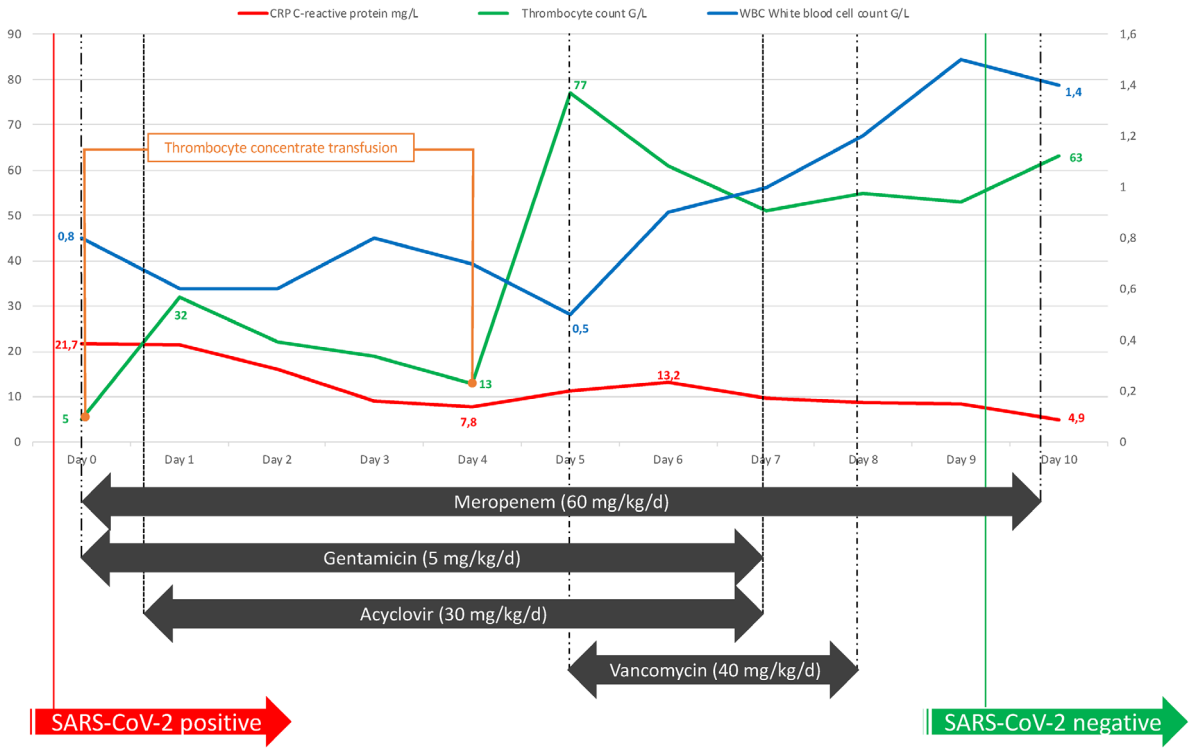

FIGURE 1 Clinical time frame

and pediatrics II). We also thank the entire nursing team of Ward X, who shifted within a week from pediatric general-surgery care to special-isolation care as their ward was repurposed, displaying great competence throughout. The patient was treated in a regular clinical setting at the University Hospital of Innsbruck (Tirol Kliniken). Routine diagnostic studies were performed through departments either of the Medical University of Innsbruck or of Tirol Kliniken.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Benoît Bernar, assistant special-isolation physician, was in charge of our patient and drafted this manuscript. Gabriele Kropshofer and Roman Crazzolara, senior pediatric oncologists, were responsible for oncologic treatment. Klaus Kapelari, active in medical crisis management in Tyrol and at the University Hospital of Innsbruck, provided Tyrolean epidemiologic data. Andrea Griesmacher is head of the Central Institute of Clinical Chemistry and Laboratory Medicine and supervised laboratory studies. Thomas Müller, head of our department, and Sabine Scholl-Bürgi, senior isolation-ward physician, both bore ultimate clinical responsibility for treatment. The manuscript was carefully reviewed and modified by all authors. All authors read and approved the final manuscript.

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REFERENCES

1. Malik YS, Sircar S, Bhat S, et al. Emerging novel coronavirus (2019-nCoV)—current scenario, evolutionary perspective based on genome analysis and recent developments. *Vet Q*. 2020;40(1):68-76.
2. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) Situation Report – 51. 2020. http://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10. Accessed date April 2, 2020.

3. Statistik Austria, Bundesanstalt Statistik Österreich. Bevölkerung am 1.1.2019 nach Alter und Bundesland – Insgesamt. 2019. https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/bevoelkerung/bevoelkerungsstruktur/bevoelkerung_nach_alter_geschlecht/023470.html. Accessed date April 2, 2020.
4. Su L, Ma X, Yu H, et al. The different clinical characteristics of corona virus disease cases between children and their families in China – the character of children with COVID-19. *Emerg Microbes Infect*. 2020;9(1):707-713.
5. Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study [published online ahead of print March 25, 2020]. *Lancet Infect Dis*. 2020. https://doi.org/10.1016/S1473-3099(20)30198-5.
6. Centers for disease control and prevention (CDC). Burden of COVID-19 and epidemiologic risk factors in children. https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html. Accessed March 26, 2020.
7. Sinha IP, Harwood R, Semple MG, et al. COVID-19 infection in children. *Lancet*. 2020;8(5):P446-P447.
8. Le service public fédéral (SPF) Santé publique, Sécurité de la Chaîne alimentaire et Environnement, Belgium. 2020. Le décès d'une jeune fille de douze ans. https://youtu.be/llFOaPFZ37Q?t=1093.
9. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337.
10. Schrappe M, et al. AIEOP-BFM 2009 protocol. Department of Pediatrics, University Hospital of Schleswig-Holstein, Campus Kiel. Complete AIEOP-BFM 2009 protocol. Maintenance therapy protocol. https://clinicaltrials.gov/ct2/show/record/NCT01117441; https://www.uni-kiel.de/all-studie/wp-content/uploads/2017/03/Therapieuebersicht_AIEOP-BFM-ALL-2009_Version-1.4.pdf; https://www.uni-kiel.de/all-studie/wp-content/uploads/2017/03/Protokoll-M_Therapiedoku_Infusionsplan_AIEOP-BFM-ALL-2009_Version-1.4.pdf

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