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LETTER TO EDITOR

SARS-CoV-2 Infection in a Child with Severe Congenital Neutropenia

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To the Editor:

The global pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has resulted in unprecedented anxiety and fear among many patient communities, especially those with underlying immunological perturbations. From the very beginning of this novel virus outbreak in the community, clinical immunologists were on high alert to understand the natural course of illness and identify optimal management protocols in patients with inborn errors of immunity (IEI) who developed SARS-CoV-2 infection [1, 2]. Studying the natural course of SARS-CoV-2 infection in patients with IEI would reveal the significance of underlying redundant immunological pathways in pathogenesis of infection. Recent studies have shown that the risk of acquiring SARS-CoV-2 infection and infection-related mortality rates in patients with IEI is similar to the general population. However, a particular group of patients with IEI also had a severe infection and fulminant course. In this context, we share our experience of SARS-CoV-2 infection in a child with severe congenital neutropenia (SCN).

Case Details

A 20-month-old male child presented to our hospital with fever, ulcers in right parotid and perianal regions, and breathing difficulty for 7-day duration (Fig. 1a). He was symptomatic from 2 months of age in the form of recurrent pneumonia and otitis media, for which he received multiple courses of oral and intravenous antibiotics. The child had no previous history of oral or cutaneous ulcers. On examination, he was febrile (103°F), tachypneic, and maintained oxygen saturation of 91% in room air that improved to 98% with nasal prongs oxygen support (40% FiO_2). Chest radiograph showed bilateral infiltrates (left > right) (Fig. 1b). His blood counts showed persistently low absolute neutrophil counts (ANC) with monocytosis. Pus culture from ulcers grew *Pseudomonas aeruginosa*. Blood and bone marrow cultures were sterile. Bone marrow examination revealed a marked reduction in neutrophil precursors and eosinophilia (Fig. 1c–f). Immunological investigations showed hypergammaglobulinemia (serum IgG-19.47 g/L) and normal lymphocyte subsets. CD40 ligand expression in stimulated T-cells and the proportion of switched and unswitched memory B cells were normal compared to control.

Nasopharyngeal aspirate for SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) came positive on day 3 hospital stay. He required oxygen support (40% FiO_2) and was started on intravenous meropenem that was continued for the next 6 weeks. Granulocyte colony-stimulating factor (G-CSF) was started at a dose of 5 µg/kg/day on day 5 that was gradually hiked up to 20 µg/kg/day by day 25 (Fig. 2). The child became afebrile and oxygen-independent on day 7; however, ulcers increased over time requiring surgical debridement. An increase in ANC was achieved only at 20 µg/kg/day of G-CSF. Nasopharyngeal swabs showed positivity for SARS-CoV-2 by RT-PCR until day 35 of illness, though he did not have any respiratory complaints after day 7. He was kept under isolation care for the first 65 days. The nasopharyngeal PCR for SARS-CoV-2 was repeated at days 66 and 69, and it was negative. Molecular analysis revealed

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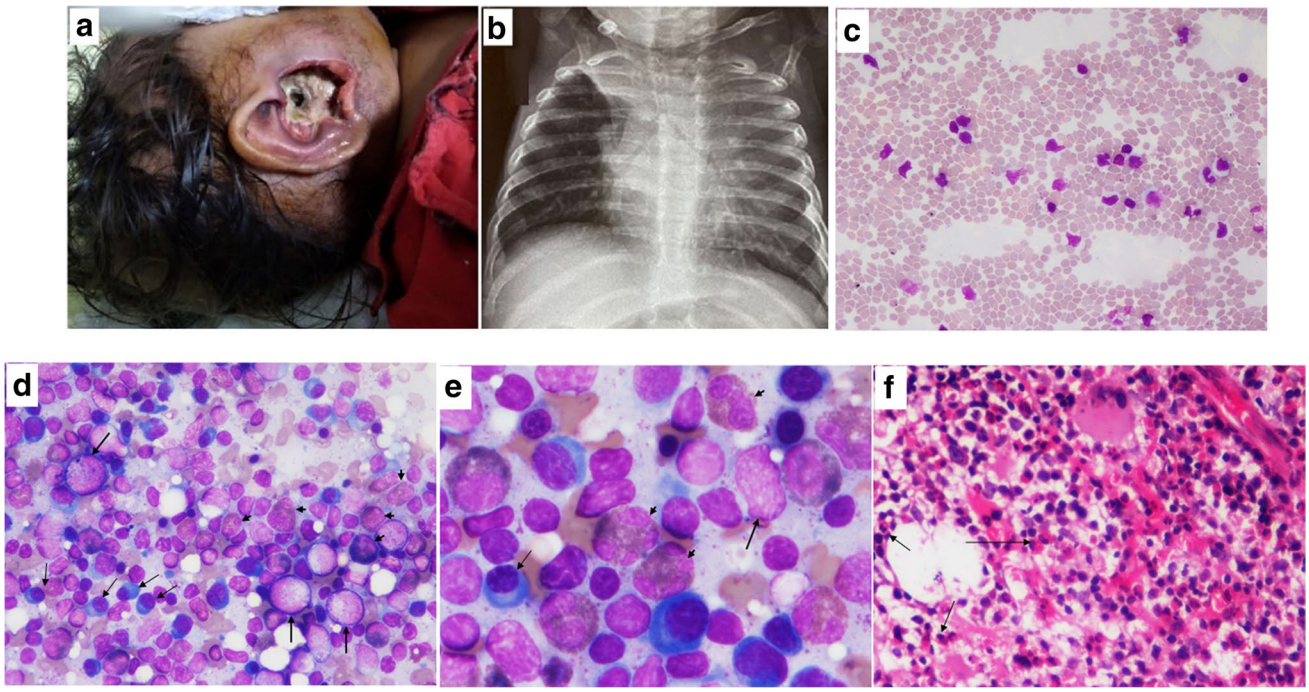

Fig. 1 **a** Ulceration in the right parotid area. **b** Chest radiograph showing bilateral infiltrates (left > right). **c** Peripheral blood smear showing leukocytes comprising mostly of monocytes and lymphocytes with marked paucity of neutrophils (May Grunwald-Giemsa stain, magnification × 20). **d**, **e** Bone marrow aspirate showing increased eosinophils and its precursors (small arrows), increased plasma cells (thin arrows), and marked paucity of neutrophils but presence of myelocytes (thick arrows) (May Grunwald-Giemsa stain, magnification × 40 and × 100 respectively). **f** Bone marrow trephine section showing normocellular marrow spaces with increase in eosinophils and its precursors (arrows) and paucity of neutrophils (hematoxylin and eosin stain, magnification × 40)

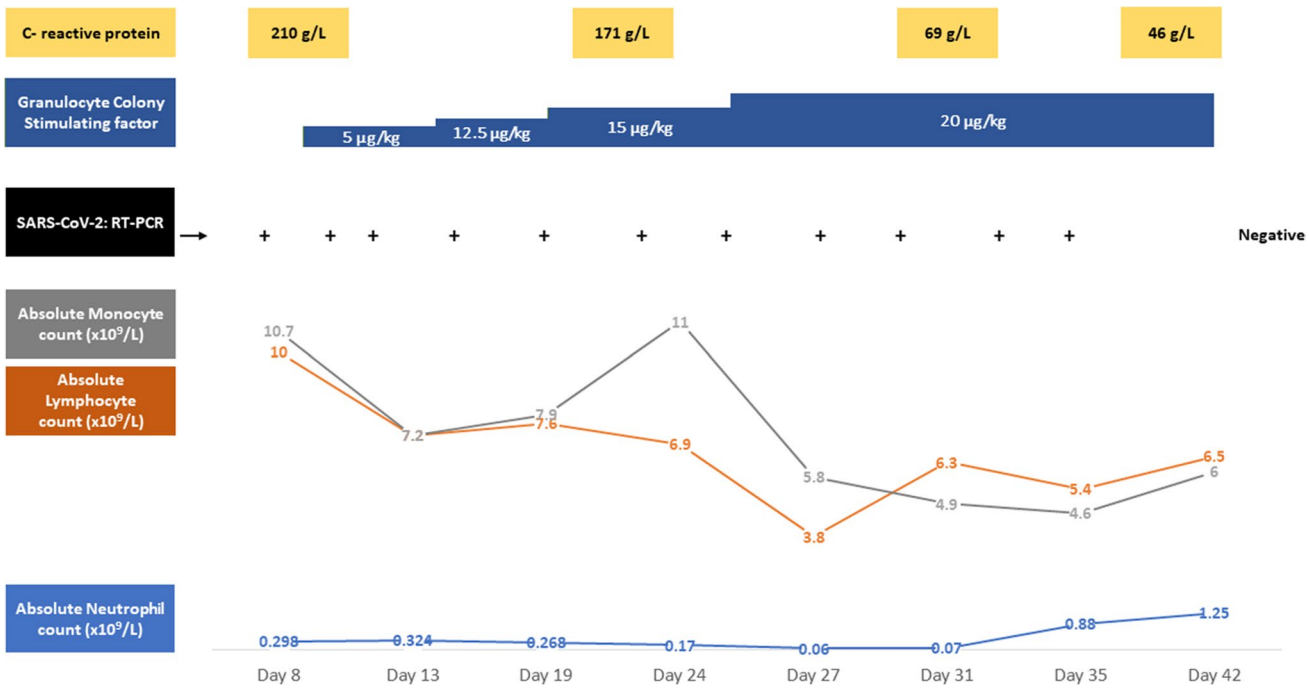

Fig. 2 Timeline of the clinical course showing the trend of absolute neutrophil, lymphocyte, and monocyte counts; C-reactive protein levels; dose of G-CSF therapy used; and serial nasopharyngeal RT-PCR results for SARS-CoV-2

a known de novo pathogenic heterozygous variant in exon 5 of *ELANE* [c.457G > C (p.Ala153Pro)]. Both the parents had normal complete blood count, including absolute neutrophil counts. Sanger sequencing of the parents did not reveal the pathogenic variant in *ELANE* identified in the child.

One health care worker (resident) who did an oral cavity examination of this patient on day 3 of hospital stay developed a mild SARS-CoV-2 infection. The caregiver mother, who was involved in the child's care, underwent testing for SARS-CoV-2 RT-PCR that turned out to be negative.

Discussion

We report a patient with severe congenital neutropenia who developed SARS-CoV-2 infection. To the best of our knowledge, ours is the first report of a patient with IEI from the Indian subcontinent who developed SARS-CoV-2 infection. Patients with SCN usually have preserved anti-viral defense mechanisms [3]. Ho et al. have shown that a patient with hyper IgM syndrome with preexisting neutropenia had a mild disease course [4]. A multi-centric study by Meyts et al. suggested neutrophil had a minimal role for immunity against SARS-CoV-2 infection based on the observation that children with chronic granulomatous disease (CGD) had a mild disease course of SARS-CoV-2 infection [1]. The authors also showed that the severity of disease and outcome among children with IEI with SARS-CoV-2 infection was similar when compared to immunocompetent host [1]. Our patient with SCN also had a less aggressive disease course of SARS-CoV-2 infection. He required oxygen support only for the first 7 days, and he did not require mechanical ventilation, inotropes support, or other therapies like remdesivir, steroids, and intravenous immunoglobulin.

The median duration of viral shedding in immunocompetent children is 13 days [5]; however, our child had a prolonged viral shedding for 35 days. The formation of neutrophil extracellular traps (NETs) has been implicated in the immunopathogenesis of SARS-CoV-2 infection [6]. A less severe disease course in our patient can be explained by reduced formation of NETs in the setting of neutropenia. However, the exact role of neutrophils in the clearance of SARS-CoV-2 is unclear, and further studies are needed to explore any relation of prolonged viral shedding in the context of neutropenia. Though the infectivity of the virus that shed for a prolonged period is not known, this aspect must be explored in future studies in patients with PIDs as people with prolonged shedding of live virus may pose a risk of active community transmission. Recent studies have also shown prolonged shedding of active virus in 2 patients with humoral immunodeficiency. While one had X-linked agammaglobulinemia, the other had secondary hypogammaglobulinemia due to chronic lymphocytic leukemia [7, 8].

Usually, in an immunocompetent host, lymphopenia with neutrophilic leukocytosis has been noted with SARS-CoV-2 infection [9]. In our child with SCN, neutrophil counts further dropped during the initial stage of SARS-CoV-2 infection. Little is known about blood cell changes in patients with preexisting cytopenia and concomitant infection with SARS-CoV-2. Nevertheless, it is essential to emphasize general hygiene, avoid contacts in groups, use face masks, and postpone routine health check-ups unless deemed necessary for children with SCN so that they do not acquire SARS-CoV-2 infection [3].

Granulocyte-monocyte colony-stimulating factor (GM-CSF) helps to clear the infection by recruiting macrophages in the inflamed site [10]. A trial with GM-CSF is ongoing in patients with SARS-CoV-2 infection with respiratory failure [11]. On the other hand, the use of G-CSF in febrile neutropenia has been reported to result in cytokine storm or respiratory worsening in the presence of active SARS-CoV-2 infection in adult patients with malignancies [12]. Several other studies have also shown elevated serum levels of G-CSF during cytokine storm of SARS-CoV-2 infection [10]. However, we decided to use G-CSF in our patient as he had severe neutropenia and *P. aeruginosa* infection. With the gradual escalation of G-CSF dose and rise in neutrophil counts, we did not note any form of clinical worsening of symptoms in the child. Our case provides preliminary evidence for the safe use of G-CSF in patients with SCN and active SARS-CoV-2 infection.

Declarations

Conflict of Interest The authors declare no competing interests.

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