Introduction

The coronavirus disease 2019 (COVID-19) pandemic has led to new challenges for healthcare professionals. Patients with cancer are known to be at higher risk of severe COVID-19. Although children generally have a favorable course of COVID-19, pediatric patients with cancer potentially have a higher risk of morbidity and mortality from viral respiratory infections. Because a consistent proportion of cancers in children and adolescents are potentially curable, a key issue in case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is how to balance the risk of immunosuppression due to oncologic treatments and the risk of tumor failure in case of treatment delay or major treatment deviations.

International guidelines that help clinicians manage these situations have recently been outlined, as well as reports from initial experiences during the pandemic.

For each patient, a careful balance between the aggressiveness of the oncologic disease and the risk and severity of the viral infection should be made.

Case description

An 11-year-old boy with T-cell lymphoblastic lymphoma (stage III, Murphy/St. Jude) was treated with intravenous and intrathecal polychemotherapy according to the Italian...
guidelines (after the EURO-LB02 Protocol5) starting in October 2020. On November 9, 2020, a surveillance nasopharyngeal molecular test resulted positive for SARS-CoV-2 (contemporaneous anti-SARS-CoV-2 antibody titer was negative). Despite the patient’s good clinical condition with normal physical examination and vital signs, because of the expected significant immunosuppression, he was hospitalized in order to continue the induction phase (Figure 1 [a]), as this phase is well known to be the most intense part of the treatment with a heightened risk of infectious complications.5

No antibiotic or antiviral drugs were administered except for the continuation of usual prophylaxis (oral trimethoprim-sulfamethoxazole and acyclovir); oral prednisone (60 mg/m²/d) was administered as per protocol during the induction phase. In order to reduce the risk of possible severe COVID-19, the patient received convalescent plasma (CP) on days 11 and 12 from the first positive swab.

The patient did not manifest SARS-CoV-2–related symptoms or signs of severe organ disease. He developed a transitory acute pancreatitis episode associated with hypertransaminasemia and prolonged antithrombin III deficit after being administered PEG-asparaginase (Figure 2).

A computed tomographic scan performed due to severe abdominal pain showed basal bilateral parenchymal disventilative areas without any evidence of ground-glass opacities, which was not interpreted as a consequence of the infection.

The anti–SARS-CoV-2 antibody titer (total immunoglobulin G–immunoglobulin M) was found positive 24 days after plasma administration.

After 47 days of hospitalization, the patient completed the induction phase and was discharged.
Due to the previous pancreatic and hepatic toxicity and the concomitant, persistent SARS-CoV-2 positivity, we decided to reduce the dose of methotrexate (3 g/m²) for the first administration (protocol M) (Figure 1 [b]); given the absence of toxicity, the subsequent courses were administered at full doses but reducing the infusion time to 6 hours instead of 24. Clearance of the drug was normal and no toxicity was observed.

At the time of writing this report, the child is still on treatment. His SARS-CoV-2 swab became negative 107 days after the first positive swab.

**Conclusions**

We describe the case of a child with an aggressive lymphoma and protracted SARS-CoV-2 infection. The concomitance of these two conditions led to several questions. Did immunosuppression expose our patient to the risk of a severe infection? Did continuing chemotherapy have more advantages or disadvantages? Would using one of the therapies suggested for severe COVID-19 infection be of some help? How could we distinguish between comorbidities related to the tumor and chemotherapy from those related to infection?

The few data available on the pediatric cancer population seem to suggest that in these patients, compared to adults, COVID-19 often has lesser severity or is asymptomatic. Although the limited information does not yet allow creation of guidelines on pediatric oncologic treatments, the literature reports different experiences in SARS-CoV-2–positive children who continued chemotherapy.6,7 A case series on 15 Spanish children with cancer and COVID-19 reported a mild course of the disease, with only 13% requiring oxygen and a few receiving specific therapies; 60% of patients did not delay chemotherapy.6 Conversely, a recent study of the French Society of Pediatric Oncology reported a less encouraging experience in 37 patients with cancer and COVID-19: 76% of patients were symptomatic for SARS-2-CoV infection and 65% had received chemotherapy a month prior to COVID-19 diagnosis. A total of 14% required intensive care unit admission because of COVID-19 (2/5 had undergone autologous stem cell transplantation within 2 months prior to COVID-19 diagnosis) and 1 died.7

Immunosuppression could be associated with a prolonged infection and delayed viral clearance,8 so waiting for a negative swab to resume treatments could lead to significant delays and reductions in the dose density/intensity crucial for many pediatric cancers. If children and young adults treated for cancer may be at risk for severe COVID-19 disease, and should be closely monitored, it seems desirable to continue oncologic treatments to prevent any delay that may negatively affect the prognosis.3

In our patient, the absence of virus-related symptoms prevented us from starting any specific treatment for COVID-19. We decided to administer CP, even though the data on its efficacy were discordant9,10 due to persistent positive nasopharyngeal swab tests after 11 days and the absence of anti–SARS-CoV-2 antibodies. The state of immunodepression justified the late antibody response. Several trials failed to demonstrate clinical improvement by CP administration compared to placebo9; however, a recent report showed that early administration of high-titer CP against SARS-CoV-2 to mildly ill infected patients significantly reduced the progression of COVID-19.11 Starting from these considerations and following the favorable experience with CP in adult patients with COVID-19 and severe humoral deficiency,10 we treated our patient with two courses of CP to prevent the progression of infection, while continuing chemotherapy.

After some time, the anti–SARS-CoV-2 antibody titer of our patient became measurable. We cannot assert with certainty whether seroconversion occurred owing to the CP but we feared that the child's immune system was too compromised to independently guarantee the production of antibodies.10

Since the first positive swab, the clinical course of the patient was generally regular. We had doubts twice on whether the unexpected manifestations that we observed were of iatrogenic or infectious origin. The acute pancreatitis we observed could be due either to the therapy with PEG-asparaginase for lymphoma or to SARS-CoV-2 infection, as reported in literature.12,13 We also observed a prolonged antithrombin III deficiency, which is known to...
be associated with asparaginase and PEG-asparaginase,\textsuperscript{12} but in our case was more severe and more protracted than expected. Certainly the infection could have played a role, also considering the evidence on thrombotic alterations related to COVID-19.\textsuperscript{14}

Overall, the management of the child was not complicated by the infection and continuing the treatment proved to be the correct choice.

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**Protection of human subjects**

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