Received: 4 April 2022 | Revised: 14 June 2022 | Accepted: 16 June 2022

DOI: 10.1002/pbc.29868

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

LETTER TO THE EDITOR

Posterior reversible encephalopathy syndrome and necrotizing enterocolitis in a pediatric patient with medulloblastoma and COVID-19 infection

To the Editor:

The 2019 novel coronavirus disease (COVID-19) pandemic due to SARS-CoV-2 infection has posed significant challenges to the pediatric oncology population. The effects on pediatric neuro-oncology patients are not yet well described. We present the case of a pediatric patient with medulloblastoma and COVID-19 who developed posterior reversible encephalopathy syndrome (PRES) and necrotizing enterocolitis (NEC).

The patient, an 8-year-old male, was diagnosed with group 4 medulloblastoma metastatic to the brain and spine in February 2021. He underwent debulking of the primary cerebellar tumor, followed by standard treatment as per Children's Oncology Group protocol ACNS0332 with proton therapy and adjuvant vincristine, followed by cycles of cyclophosphamide, cisplatin, and vincristine. His course was complicated by multiple episodes of febrile neutropenia and significant nausea/vomiting. He was diagnosed with peripheral neuropathy and bilateral foot drop following cycle 3 and started on gabapentin. There were no other known comorbidities. Post-radiation and cycle 3 chemotherapy imaging showed excellent treatment response, the latter negative for intracranial or spinal disease.

During cycle 3, the patient was admitted with a 3-day history of rhinorrhea, 1 day of fever to 101.4°F, neutropenia (absolute neutrophil count [ANC]: 100/μl), and SARS-CoV-2 positive by viral swab polymerase chain reaction (PCR). He was discharged 5 days later following count recovery. Seventeen days following diagnosis of COVID-19, the patient began cycle 4 chemotherapy. One week later (25 days following COVID-19 diagnosis), he was admitted for significant vomiting, oral mucositis, and dehydration. He was afebrile but neutropenic, and was started on vancomycin for two small abdominal sites of methicillin-resistant *Staphylococcus aureus* (MRSA) culture-positive cellulitis.

On day 7 of hospitalization, the patient was noted to have vertical nystagmus after waking. Head computed tomography (CT) showed no acute intracranial process. Magnetic resonance imaging (MRI) revealed stippled patchy enhancement along the right medial cerebellum, consistent with encephalomalacia. Oxycodone (started for mucositis-related pain) and gabapentin were both held, and the nystagmus was noted to significantly improve over the next 48 hours.

On day 9 of hospitalization, the patient developed altered mental status with staring spells, decreased muscle tone, and dysarthria. Head CT showed bilateral hypodense lesions in the parietal lobes. Blood pressure at that time was noted to be in the 130s/100s, with a peak of 146/106 (previously 120s/90), and the patient was transferred to the pediatric intensive care unit. On arrival, the patient had a generalized seizure and was emergently intubated. MRI showed extensive new patchy cortical and subcortical T2 hyperintensities, most pronounced in the parietal and occipital lobes, as well as punctate foci of petechial hemorrhage along the parietal cortex, consistent with PRES with hemorrhagic sequelae (Figure 1). Treatment with dexamethasone, 2 mg intravenous every 6 hours, was initiated. The patient tolerated extubation the following day, but had persistent altered mental status. During this time, his neutropenia resolved, and vancomycin was discontinued.

Four days after extubation (hospital day 15), the patient's oxygen requirement increased and he developed abdominal distension, bradycardia, and hypotension, necessitating re-intubation, multiple vasopressors, and the initiation of broad-spectrum antibiotics. It was at this time that the patient had a repeat nasal swab positive for SARS-CoV-2. Abdominal imaging showed multiple areas of pneumatosis consistent with NEC, and an emergent bedside laparotomy was performed (Figure S1). The cecum, ascending colon, and proximal transverse colon to the midpoint were all necrotic without perforation. He underwent a right hemicolectomy and resection of distal small bowel with temporary closure. On day 19, the patient was taken to the operative room (OR) for an additional hepatic flexure resection. On day 20, the patient was noted to have decreased responsiveness, and a CT of the brain demonstrated new multicompartmental intracranial hemorrhages, a hypoattenuating subdural fluid collection, and 3 mm of leftward midline shift. MRI showed leftward shift with resolution of the sulcal and cortical enhancement noted previously (Figure 2). Despite full cardiorespiratory support, the patient could not be adequately ventilated or perfused and, in the setting of significant intracranial insults and multisystem organ failure, the decision was made with the team and family to withdraw care. The patient died several hours later.

This case highlights several critical points of COVID-19 in a pediatric neuro-oncology patient. As has been previously described, high SARS-CoV-2 viral loads may persist longer in immunocompromised children.[1–3] In a retrospective study at Children's Hospital of Colorado, Dolan et al. found that immunocompromised children with COVID-19 had prolonged viral persistence greater than 6 weeks, with moderate to high viral load.[1] Kemp et al. described a case of increased variant emergence in an immunocompromised patient after a prolonged period of viral shedding and management with convalescent plasma.[4] Further

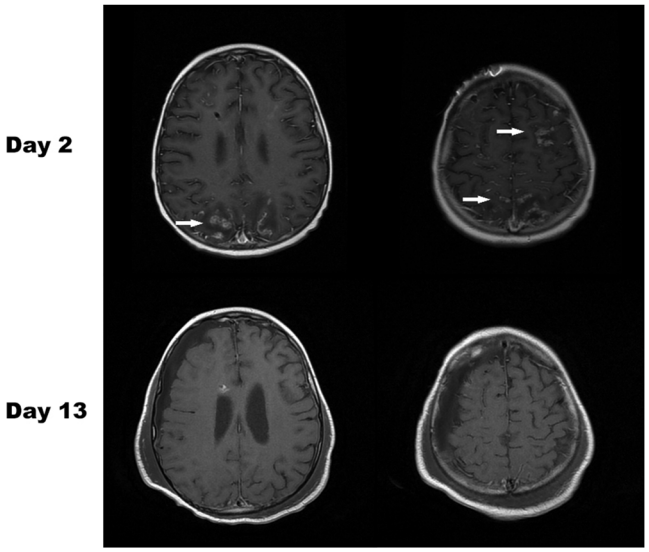

FIGURE 1 Axial T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) at two similar representative levels on days 0, 2, and 13 after positive COVID test demonstrating rapid development of cortical and subcortical T2 hyperintensities (white arrows) predominantly in the posterior parietal and occipital regions with improvement/reduction in the finding by day 13

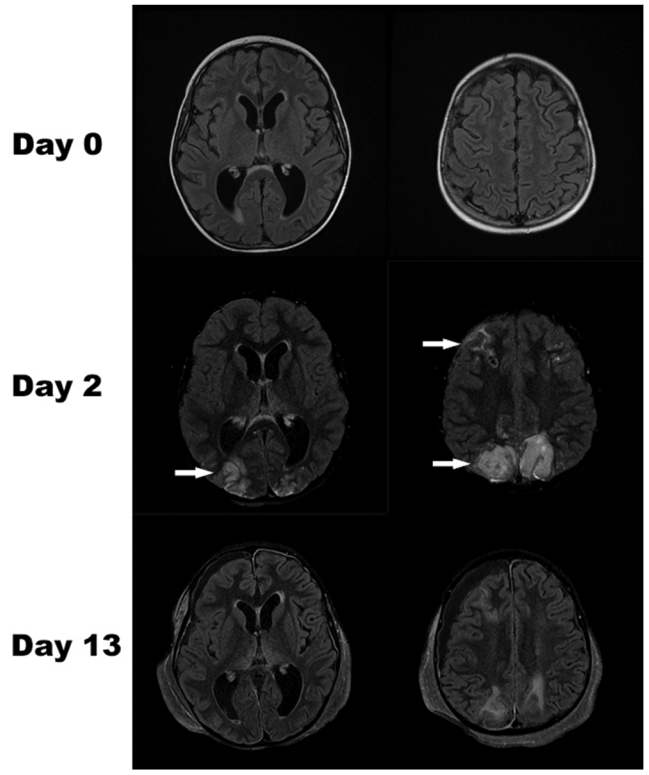

FIGURE 2 Axial postcontrast T1-weighted series at two similar representative levels on days 2 and 13 after positive COVID test showing rapid development and subsequent resolution of sulcal/cortical enhancement in regions also associated with the T2 hyperintensities noted (white arrows)

exploration is required to determine if there exists an increased risk for COVID-19-related sequelae.

Significant neurologic manifestations have been described in SARS-CoV-2-positive patients both with and without comorbidities.[5–7] In a systematic review by O'Loughlin et al., 15 cases of severe encephalopathy were identified after confirmatory testing of COVID-19, while only one of them had a pre-existing neurologic condition.[5] Case reports of PRES in both a previously healthy adult and child have also been described. In both cases, the authors cite endothelial dysfunction triggered by COVID-19 as a possible mechanism.[6,7] Radiation treatment and chemotherapy, with agents that cross the blood–brain barrier, increase vulnerability to PRES in pediatric neuro-oncology patients. Sentinel signs and risk factors, including new-onset neurologic deficits and new-onset hypertension, in this patient population should be rigorously pursued.[9] Additionally, tighter blood pressure control could be protective in such a patient.

Finally, there have been increasing reports of NEC associated with COVID-19 in pediatric and immunocompromised populations.[10–13] In a case report by Rohani et al., an otherwise healthy pediatric patient was admitted for abdominal pain, fever, nausea, and vomiting and was found to have pneumatosis intestinalis in the setting of acute COVID-19. He was medically treated for NEC with improvement.[11] Poor prognosis in NEC is tied to the presence of perforation, which can be minimized by early detection and management.[14] Clinicians should be on high alert for persistent viral load of COVID-19 and its sequelae, including PRES and NEC, in the most vulnerable pediatric patient populations.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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