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Posterior Reversible Encephalopathy Syndrome and Necrotizing Enterocolitis in a Pediatric Patient with Medulloblastoma Infected with COVID-19

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Title:

Posterior Reversible Encephalopathy Syndrome and Necrotizing Enterocolitis in a Pediatric Patient with Medulloblastoma Infected with COVID-19

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Abbreviation	Full Term
CV	COVID-19

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Abbreviation	Full Term
PRES	Posterior Reversible Encephalopathy Syndrome
NEC	Necrotizing Enterocolitis
ICC	Immunocompromised Children
PCR	Polymerase Chain Reaction
ANC	Absolute Neutrophil Count
MRSA	Methicillin-Resistant *Staphylococcus aureus*
CT	Computed Tomography
MRI	Magnetic Resonance Imaging

Conflict of Interest Statement: The authors have no conflicts of interest to disclose.

Abstract:

The COVID-19 pandemic has posed significant challenges to the pediatric oncology population. The effects of the virus on pediatric neurooncology patients are not yet well described. We present the case of a pediatric patient with medulloblastoma and SARS-CoV-2 infection (CV) who developed posterior reversible encephalopathy syndrome (PRES) and necrotizing enterocolitis (NEC). An 8-year-old male with group 4 medulloblastoma metastatic to the brain and spine underwent debulking and standard treatment. During cycle 3, he developed symptomatic CV. Seventeen days later, he began cycle 4 after appropriate count recovery. Twenty-six days after last positive CV test during a hospitalization for chemotherapy complications, the patient developed vertical nystagmus. His neurological exam quickly deteriorated with imaging supporting PRES. Repeat CV testing confirmed viral presence. The patient subsequently developed NEC after upgrading to the intensive care unit and endured multiple bedside procedures, after which the decision to withdraw support was made. This case highlights the increased risks this vulnerable population experiences and reiterates the importance of early identification and treatment of CV sequelae.

Main text:

To the Editor:

The 2019 novel coronavirus (COVID-19 due to SARS-CoV-2 infection) pandemic has posed significant challenges to the pediatric oncology population. The effects of the virus on pediatric neurooncology patients are not yet well described. We present the case of a pediatric patient with medulloblastoma and SARS-CoV-2 infection (CV) 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 essentially negative for intracranial or spinal disease.

During cycle 3, the patient presented with a 3-day history of rhinorrhea, 1 day of fever to 101.4 , neutropenia (ANC 100/microliter), and was found to be positive for CV by viral swab PCR. He was admitted to the pediatric oncology unit for 5 days and discharged following count recovery. Seventeen days following diagnosis of CV, the patient began cycle 4 chemotherapy. One week later (25 days following CV diagnosis) he was admitted for significant vomiting, oral mucositis, and dehydration. He was afebrile at the time but neutropenic and started on vancomycin for two small areas of MRSA culture-positive cellulitis on his abdomen. Following a 14-day asymptomatic period, hospital day 6 of this admission, the patient was declared "non-infectious" for CV.

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On day 7 of hospitalization, the patient was noted to have vertical nystagmus after waking. Head CT showed no acute intracranial process. MRI showed stippled patchy enhancement along the right medial cerebellum consistent with encephalomalacia that was most consistent with post-treatment change. 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 at that time 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 (Fig. 1). Treatment with dexamethasone, 2 milligrams 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 reintubation, multiple vasopressors, and the initiation of broad-spectrum antibiotics. It was at this time that the patient had a repeat nasal swab demonstrating a positive CV result. Abdominal imaging showed multiple areas of pneumatosis consistent with necrotizing enterocolitis (Fig. 3) and an emergent bedside laparotomy was performed for clinical deterioration. The cecum, ascending colon, and proximal transverse colon to the midpoint were all necrotic with no perforation. Management consisted of a right hemicolectomy and resection of distal small bowel with temporary closure. On day 19, the patient was taken to the OR for an additional hepatic flexure resection. On day 20, the patient was noted to have decreased responsiveness, so a CT of the brain was performed which demonstrated new multicompartmental intracranial hemorrhages, a hypoattenuating subdural fluid collection, and 3 mm's of leftward midline shift. MRI additionally showed leftward shift alongside resolution of the sulcal and cortical enhancement noted previously (Fig. 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 CV in a pediatric neurooncology patient. As has been previously described, high CV viral loads may persist for longer than average in immunocompromised children [1-3]. In a retrospective study at Children's Hospital of Colorado, Dolen et al found that immunocompromised children with CV had prolonged viral persistence greater than 6 weeks and 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]. The major implications that require further exploration of these findings include an increased risk for CV-related sequelae and transmission to close contacts including health care providers.

Significant neurologic manifestations have been described in CV-positive patients both with and without comorbidities [5-7]. In a systematic review by O'Loughlin et al, fifteen cases of severe encephalopathy were identified after confirmatory testing of CV, while only one of them had a preexisting 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 CV as a possible mechanism [6-7]. Radiation treatment and chemotherapy with agents known to cross the blood-brain barrier are known to increase vulnerability to PRES in pediatric neurooncology 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, it could be argued tighter blood pressure control could be protective in such a vulnerable patient.

Finally, there have been increasing reports of NEC associated with CV in both pediatric and immunocompromised populations [10-13]. In a case report by Rohani et al, an otherwise healthy pediatric patient was

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admitted for abdominal pain, fever, nausea and vomiting and found to have pneumatosis intestinalis in the setting of acute CV. He was medically treated for necrotizing enterocolitis 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.

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Figure Legend:

Figure 1: Axial T2-FLAIR at two similar representative levels on Day 0, Day 2, and Day 13 after positive COVID test demonstrating rapid development of cortical and subcortical T2 hyperintensities (white arrows)

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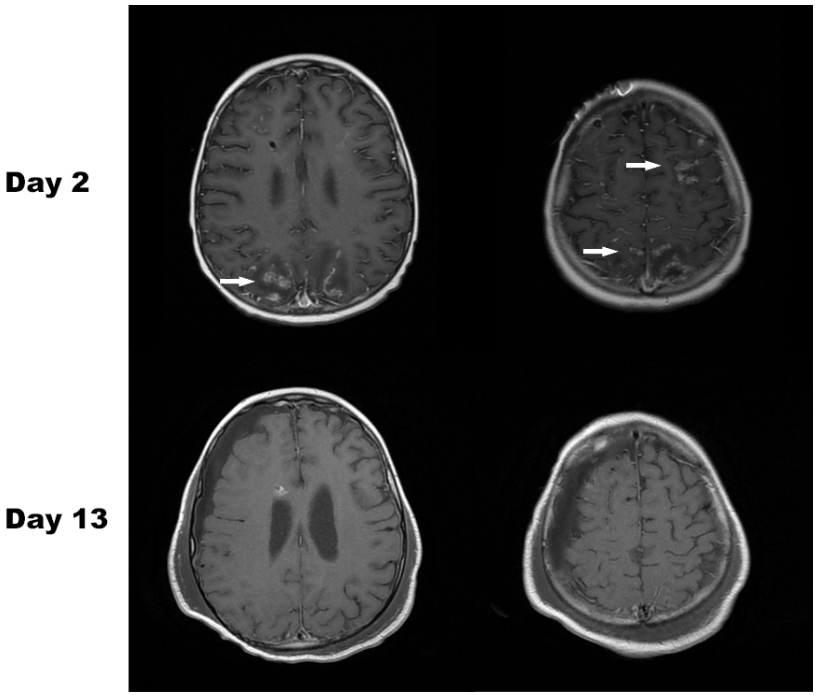
predominantly in the posterior parietal and occipital regions with improvement/reduction in the finding by Day 13.

Figure 2: Axial postcontrast T1 weighted series at two similar representative levels on Day 2 and Day 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).

Figure 3: Abdominal radiograph demonstrates dilated loops of bowel several of which contain intramural air (white arrow) compatible with necrotizing enterocolitis (NEC).



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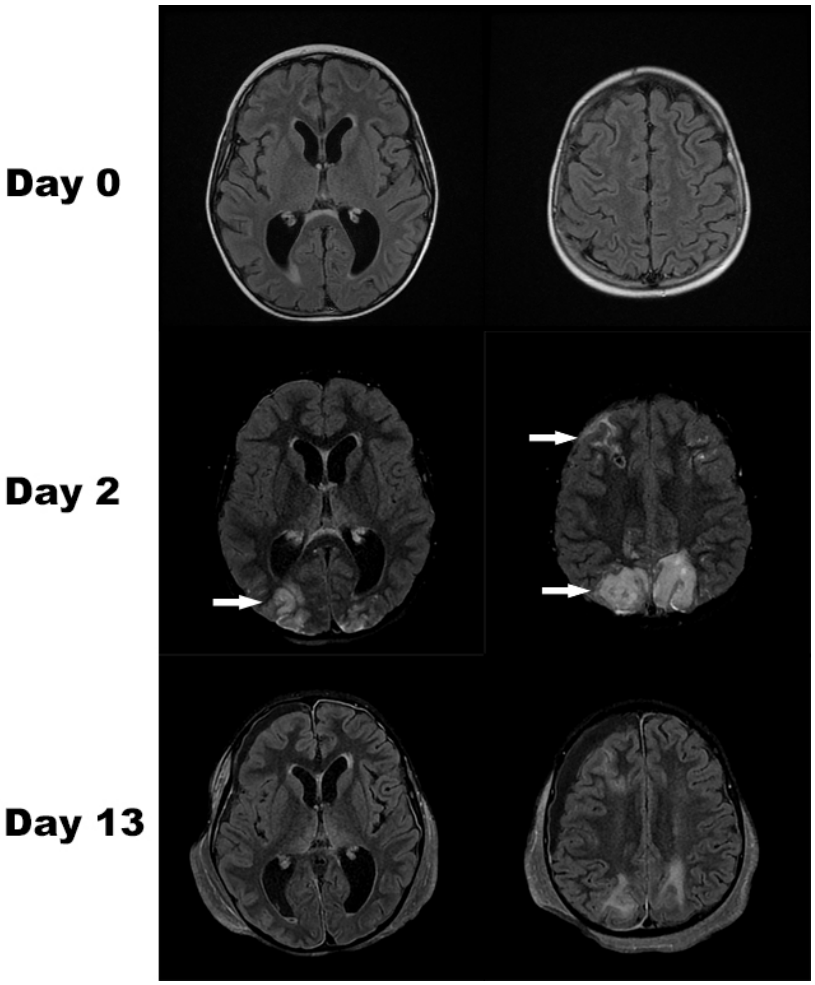

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