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Pediatric CNS-isolated hemophagocytic lymphohistiocytosis with brain hemorrhages: a case report

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Abstract

Background Hemophagocytic lymphohistiocytosis (HLH) is an inherited syndrome characterized by immune dysregulation. Central nervous system (CNS)-isolated disease is a rare presentation of familial HLH. We present a case of pediatric CNS-isolated HLH with a presentation complicated by unusual hemorrhagic intraparenchymal lesions.

Case Presentation A 15-year-old male presented with ataxia and MRI findings of multiple hemorrhagic lesions in his cerebral white matter, brainstem, and cerebellum, suggestive of vasculitis. After failing to improve with steroids and plasmapheresis, and progression to acute neurologic decompensation, new brainstem hemorrhages were noted. Further workup revealed 2 *PRF1* mutations, confirming a diagnosis of familial CNS-HLH. He was later found to have a platelet granule defect, explaining his atypical neuroradiologic findings. The patient received treatment per the HLH-1994 protocol and underwent stem cell transplantation. Two years post-transplant, his perforin expression is nearly normal and his neurologic deficits have significantly improved.

Conclusions This case illustrates the variability in presentation of isolated CNS-HLH. Although rare, it is important to include this diagnosis on the differential in patients with CNS hemorrhagic lesions. If initial diagnostic studies remain inconclusive or response to early treatments is poor, CNS-HLH should be considered, as delay in diagnosis and treatment significantly affects morbidity and mortality.

Keywords Hemophagocytic lymphohistiocytosis, CNS involvement, Pediatric, Hemorrhage, Case report

Background

Hemophagocytic lymphohistiocytosis (HLH) is an inherited syndrome characterized by immune dysregulation, with central nervous system (CNS)-isolated disease a rare presentation of familial HLH. Isolated CNS-HLH was first described in 2005 in a young child found to have histologic features of HLH on brain biopsy in the absence of other systemic criteria of HLH [1]. Since then, case reports of isolated CNS-HLH have been published, although a common diagnostic challenge is the absence of systemic HLH symptoms and the overlap of symptoms with other neuroinflammatory disorders [2]. Neuroradiologic features in patients are nonspecific, with the most

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common finding being nonspecific white matter lesions, particularly with cerebellar involvement [3–5]. Consequently, there is typically a delay in initiation of treatment, with the average time to diagnosis reported to be 19.5 months [1].

Patients with familial HLH are known to carry mutations in one of several different genes, with mutations in the *PRF1* gene affecting perforin expression in T cells and NK cells being the most common in CNS-HLH [2, 3]. It is still unclear why patients with CNS-HLH do not present with systemic symptoms, although one hypothesis is that these patients harbor additional genetic modifying factors which predispose them to neuroinflammatory events [2]. Here, we discuss a 15-year-old male who presented with ataxic gait and atypical MRI findings of multiple hemorrhagic lesions, suggesting an underlying vasculitis. He did not improve with steroid treatment, and after further workup he was found to harbor 2 *PRF1* mutations, confirming a diagnosis of familial CNS-HLH. He was ultimately found to have a platelet granule defect as well, which explained his atypical neuroradiologic findings. Manuscript reporting follows CARE guidelines [6].

Table 1 Summary of Lab Results

Test	Value	Refernce	Interpretation
WBC	5.5	4.0–11.0 x10^9/L	Normal
Hb	14.7	13.5–17.5 g/dL	Normal
RBC	5.43	4.5–5.9 x10^12/L	Normal
Hematocrit	45.3	41.5–50.4%	Normal
PLT	185	150–450 x10^9/L	Normal
Ferritin	18.9	30–400 ng/mL	Low
Triglycerides	172	< 150 mg/dL	High
Fibrinogen	179	200–400 mg/dL	Low
ALT	16	7–56 U/L	Normal
AST	34	10–40 U/L	Normal
CRP	< 0.5	< 1.0 mg/L	Normal
ESR	7	0–15 mm/hr	Normal
sIL2R	600	137–838 U/mL	Normal
CD56 BRIGHT	1.8	1.7–13.4%	Normal
PERF POS NK	1	79–94%	Low
PERF MCF NK	28	98–181 MCF	Low
PERF POS CD8	0	2–15%	Low
GR B POS NK	97	80–98%	Normal
GR B POS MCF	719	152–825 MCF	Normal
GR B CD8	85	0–61%	High
CD107A POS NK	30	11–35	Normal
CD107A MCF	1524	207–678	High
FHL3	Thr450Met; Pro187Ser		Pathogenic; Likely Pathogenic
FHL3 (mother)	Pro187Ser		Likely Pathogenic
FHL3 (father)	Thr450Met; Pro188Leu		Pathogenic; Variant Unknown Significance

Case presentation

A previously healthy 15-year-old male presented to the emergency room with a history of 2.5 months of unsteady gait. Initially he noticed difficulty kicking a ball while playing soccer, but his symptoms progressed to gait imbalance and frequent tripping. He was previously seen by Orthopedic Surgery, who performed hip and leg x-rays, which were normal. On review of systems, he also endorsed bilateral tinnitus and urinary hesitancy. On arrival, his temperature was 37 °C, blood pressure 132/71 mm Hg, pulse 94 beats per minute, respiratory rate 19 breaths per minute, and oxygen saturation 94% while breathing room air. Physical examination was notable for dysmetria and intention tremor–more pronounced on the right side–with finger to nose testing, hyperreflexia of bilateral patellar reflexes, and multiple beats of ankle clonus bilaterally. He also exhibited decreased sensation of the right toe and right lower leg with normal sensation at the thighs. He was unable to stand on one foot at a time and was ataxic, with a wide-based gait veering to the right side. Labs included WBC 5.5×10^9/L, Hb 14.7 g/dL, RBC 5.43×10^12/L, hematocrit 45.3%, PLT 185×10^9/L, ferritin 18.9 ng/mL (L), triglycerides 172 mg/dL (H), fibrinogen 179 mg/dL (L), ALT 16 U/L, AST 34 U/L, CRP < 0.5 mg/L, and ESR 7 mm/hr (Table 1).

The patient was admitted for further workup. MRI of the brain and whole spine with and without contrast demonstrated multifocal enhancing hemorrhagic lesions in the cerebral white matter, brainstem, cerebellum, and spinal cord, with the largest area of hemorrhage in the left aspect of the pons (Figs. 1, 2 and 3). These areas of abnormal postcontrast enhancement demonstrated high signal intensity on diffusion weighted imaging, most of which does not demonstrate appreciable ADC correlates, favored to represent T2 shine through artifact. Few smaller scattered areas of true restricted diffusion are noted in these regions of postcontrast enhancement, which are favored to represent cytotoxic edema related to parenchymal injury. Follow-up MRA head without contrast to investigate for vasculitis showed no occlusive lesion and no intracranial aneurysm. CSF studies were unrevealing for an infectious or malignant cause. Given the concern for a demyelinating process, he was treated with 60 mg methylprednisolone daily.

On hospital day 10, after mild improvement in his gait, he experienced an acute change characterized by sudden loss of sight and hearing, new left-sided facial droop, and dilated pupils, followed by loss of consciousness. A CT and MRI showed new large areas of intraparenchymal hemorrhage including the dorsal right pons (Fig. 1) and along the midbrain near the cranial nerve III nuclei. There was local mass effect upon the adjacent fourth ventricle. The patient was bradycardic and hypertensive

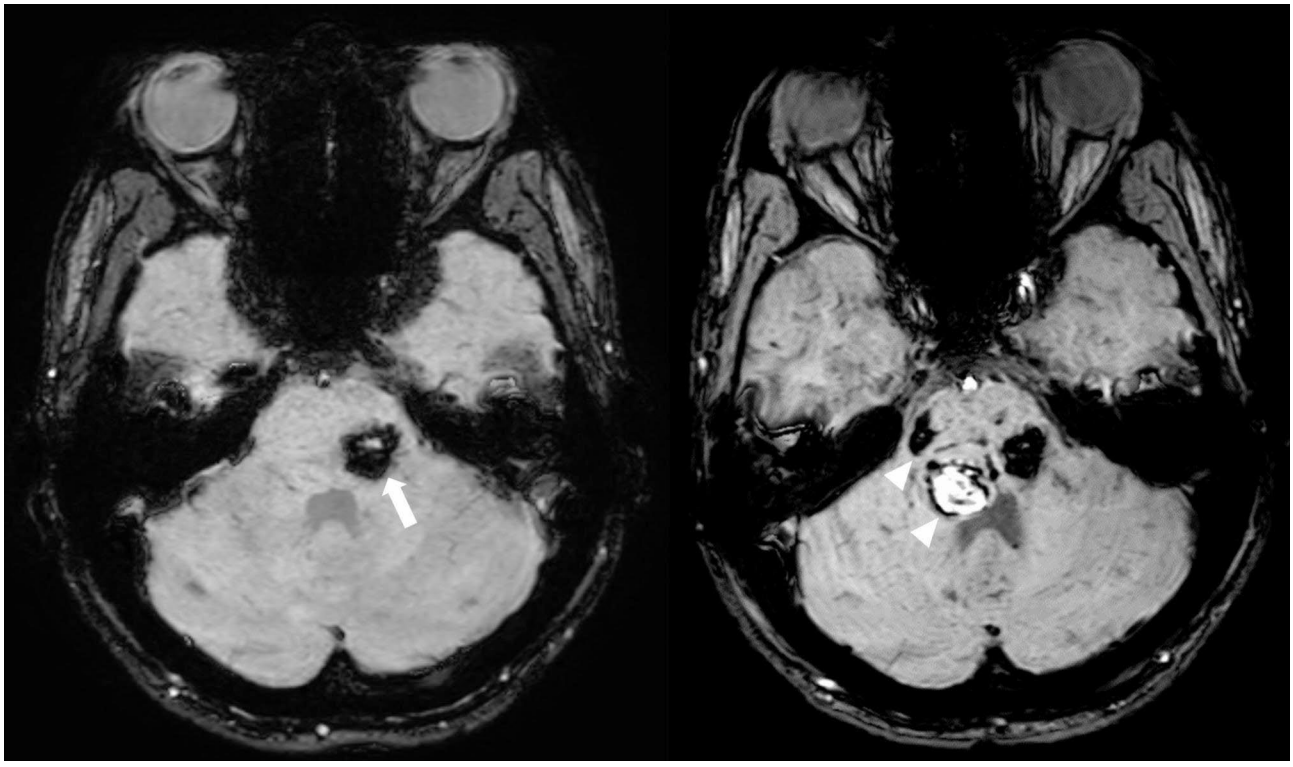

Fig. 1 Left – Initial MRI: Axial Susceptibility Weighted Image (SWI) at the level of the brainstem demonstrates a prominent area of susceptibility related signal loss within the left aspect of the pons compatible with hemorrhage (white arrow). Right – Follow-up MRI 2 weeks later: Axial SWI at the same level demonstrates new prominent areas of hemorrhage within the right aspect of the pons (white arrowheads)

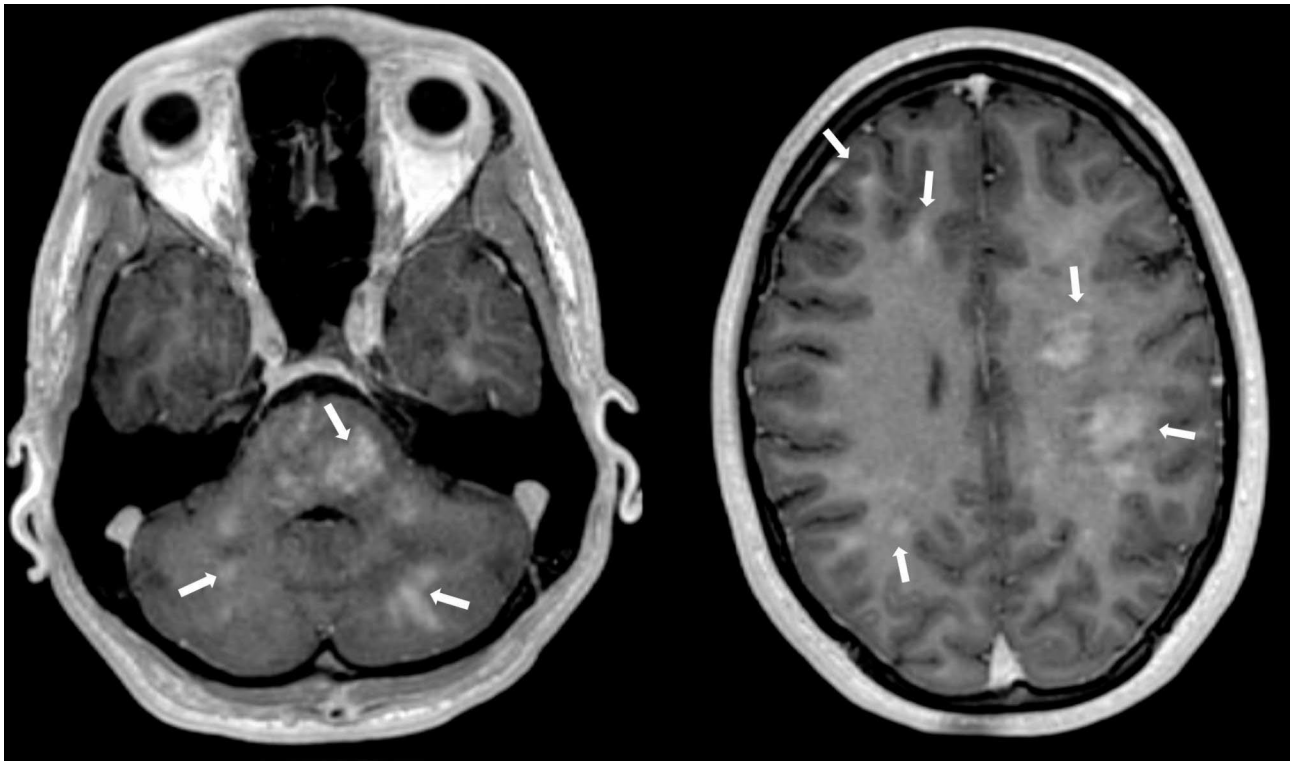

Fig. 2 Axial contrast enhanced images of the brain demonstrate multifocal patchy areas of enhancement within the pons, cerebellum, and left greater than right cerebral hemispheres (white arrows)

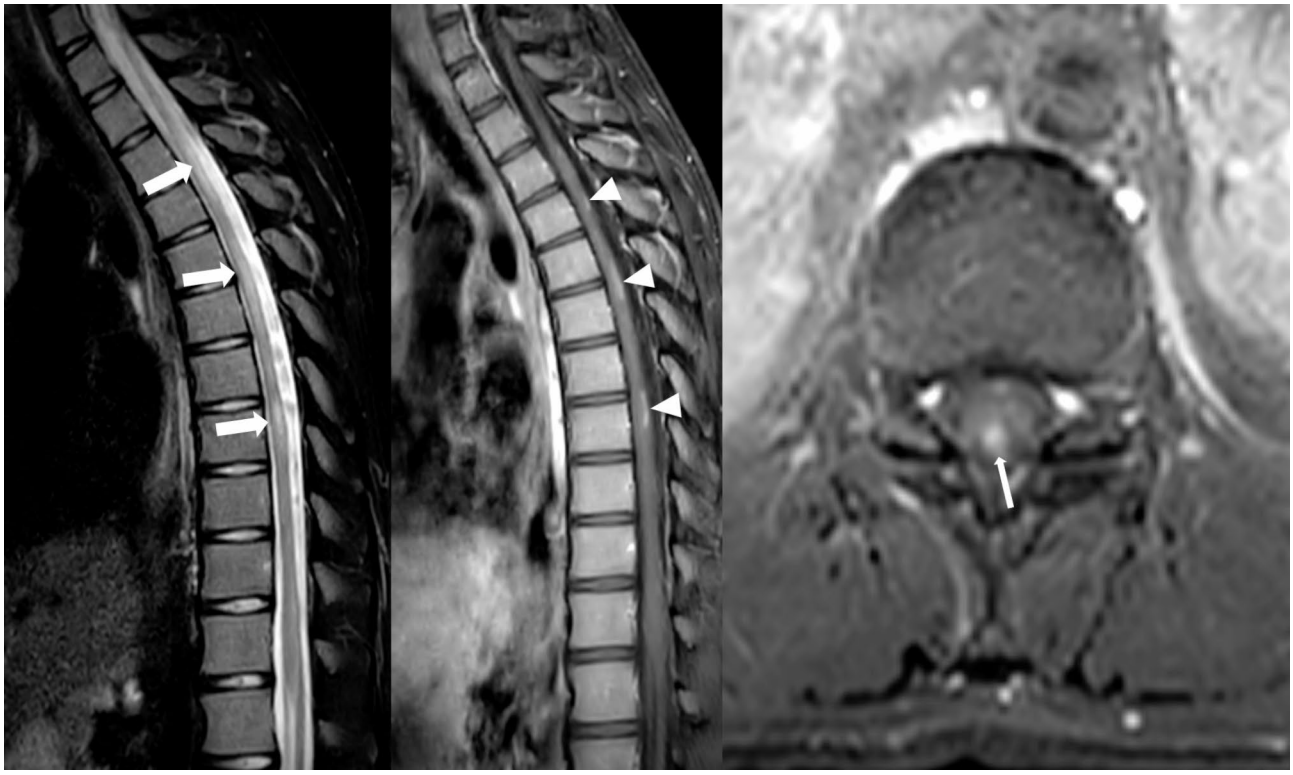

Fig. 3 Left – Sagittal T2 Dixon image of the thoracic spine demonstrates multifocal spinal cord signal abnormality (white arrows). Center – Sagittal T1 contrast enhanced images of the thoracic spine demonstrates multifocal spinal cord signal abnormality (white arrowheads). Right – Axial T1 contrast enhanced image of the thoracic spine demonstrates an abnormal focus of enhancement within the spinal cord (white arrow)

following the event. A drain was placed for monitoring of intracranial pressure and for potential to decrease and treat increased pressure with cerebrospinal fluid drainage. The patient was transferred to the pediatric intensive care unit, and an external ventricular drain was placed. When the patient was stabilized 3 days later, his exam was notable for loss of ability to vocalize but intact comprehension, left pupil dilation, left gaze preference with inability to cross the midline and not overcome by head maneuvers, right facial droop with incomplete right eye closure, and generalized decreased strength throughout the body. He received a course of plasmapheresis for possible vasculitis; however, this had minimal improvement on his symptoms.

Testing of Perforin/Granzyme B and cd107a Mobilization was sent to Cincinnati Children's and revealed that his perforin/Granzyme B expression was essentially absent. A Familial Hemophagocytic Lymphohistiocytosis gene mutation analysis was also sent to Cincinnati Children's and he harbored 2 heterozygous *PRF1* mutations: *Thr450Met*, a pathogenic variant associated with familial HLH and *Pro187Ser*, a variant of unknown significance at the time but then upgraded to likely pathogenic because of this patient's case leading to the diagnosis of CNS-HLH. PRF1 gene sequencing for the father revealed two heterozygous PRF1 mutations: *Thr450Met*, the same pathogenic variant as his son and *Pro188Leu*, a different variant of unknown significance. The mother shared the other likely pathogenic heterozygous PRF1 mutation Pro187Ser (Table 1). He began treatment as per the HLH-1994 protocol and experienced significant improvement in his neurologic exam. He underwent stem cell transplantation following reduced toxicity myeloablative conditioning with alemtuzumab (cumulative dose 1 mg/kg on days −14 through −10), fludarabine (30 mg/m2/day on days −8 through −3), and busulfan (cumulative AUC target 70 mg*h/L on days −5 through −3). His donor was a haploidentical aunt who harbored one of the PRF1 mutations (*Pro187Ser*) but was otherwise healthy. He received post-transplant cyclophosphamide, tacrolimus, and mycophenolate for graft versus host disease prophylaxis. His post-transplant course was complicated by mild engraftment syndrome, anaphylaxis to platelet transfusions, herpes simplex virus 1 lesions of the oropharynx, and mild hemorrhagic cystitis due to BK virus.

While preparing for transplant, he was also diagnosed with a platelet granule defect via platelet function testing. His donor had normal platelet function testing, and his granule defect was corrected post-transplant. Now 2 years post-transplant, his perforin expression is nearly normal and his neurologic deficits have significantly improved. His exam now demonstrates full

extraocular movements with left gaze nystagmus, 5/5 strength throughout, diminished right-sided face and body sensation, and a wide-based gait with right steppage.

Discussion and conclusions

This is a case of pediatric CNS-isolated HLH with an unusual presentation complicated by excessive intracranial bleeding secondary to a platelet function defect. Differentials that can present similarly include vasculitis, acute hemorrhagic leukoencephalitis, acute disseminated encephalomyelitis (ADEM), and posterior reversible encephalopathy syndrome (PRES). Vasculitis typically presents with systemic inflammation, can show small to medium vessel wall narrowing or beading on MR angiography and demonstrate small infarcts bilaterally at various stages on MRI, and tends to show a favorable response to steroids. Acute hemorrhagic leukoencephalitis, another condition with high morbidity that usually occurs after an infectious illness and also has a good response to steroids or immune modulation. ADEM may present with T2/FLAIR hyperintense typically subcortical white matter lesions with surrounding edema and with possible ring enhancement on post-contrast T1-weighted images. Posterior reversible encephalopathy syndrome (PRES) classically demonstrates subcortical white matter hyperintense signal on T2/FLAIR typically in the parietal-occipital region. Diffusion weighted imaging shows no restriction. The hemorrhagic findings on his initial scans further obscured an already-unusual diagnosis, and the true cause was only discovered after the patient failed to improve with initial vasculitis-type therapy resulting in reconsidering the differential diagnosis and ultimately to send the perforin testing looking for CNS-HLH. The symptoms associated with CNS-HLH are broad and suggest a wide differential, with the most common findings being cerebellar involvement and MRI with nonspecific white matter lesions [3–5]. However, neuroradiologic findings can vary, including ring enhancing masses [7]. Additional imaging appearances of CNS-HLH include multifocal T2-weighted/FLAIR hyperintensities with postcontrast enhancement and microhemorrhage in the brain, CLIPPERS-like (Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids) pontine and cerebellar nodular/patchy T2-weighted/FLAIR hyperintensity with postcontrast enhancement, and leptomeningeal involvement [8]. Larger areas of hemorrhage can be seen in CNS-HLH, however is not considered diagnostic criteria as it is exceedingly rare. Spinal cord involvement in HLH has been reported but appears to be even more rare than large areas of hemorrhage [9]. The nonspecific imaging findings of cerebral, cerebellar, and spinal cord signal abnormality and enhancement combined with larger areas of pontine hemorrhage add to the difficulty in diagnosing CNS-HLH based on imaging. This case illustrates the variability in presentation of CNS-HLH and the importance of having this diagnosis in the differential if response to initial treatments is not adequate or if diagnostic studies are not conclusive, as delay in treatment can significantly affect morbidity and mortality.

Abbreviations

ADEM	Acute disseminated encephalomyelitis
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CLIPPERS	Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids
CRP	C-reactive protein
CNS	Central nervous system
ESR	Erythrocyte sedimentation rate
FLAIR	Fluid-attenuated inversion recovery
Hb	Hemoglobin
HLH	Hemophagocytic lymphohistiocytosis
MRI	Magnetic resonance imaging
PLT	Platelets
PRES	Posterior reversible encephalopathy syndrome
RBC	Red blood cells
WBC	White blood cells

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Author contributions

MB: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. HT: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. SB: Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. AB: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data. ND: Drafting/revision of the manuscript for content, including medical writing for content. EF: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

We, the authors confirm that we have received written informed consent to disclose from both the minor patient and from his parent/guardian. They consent to give consent for images or other clinical information relating to his case to be reported in a medical publication. They understand that his name and initials will not be published and that efforts will be made to conceal his identity, but that anonymity cannot be guaranteed. They understand that the material may be published in a journal, website or other form of publication. As a result, they understand that the material may be seen by the general public. They understand that the material may be included in medical books. They have read the manuscript and reviewed all images, photographs, submissions, and videos that will be included with the manuscript if published.

Competing interests
The authors declare no competing interests.

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