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CASES WITH A MESSAGE

Acute pancreatitis and macrophage activation syndrome in pediatric systemic lupus erythematosus: case-based review

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Abstract

Pancreatitis is uncommon in systemic lupus erythematosus (SLE) and is rarely reported in children, possibly being related to macrophage activation syndrome (MAS). The incidence of MAS in children with lupus pancreatitis is unknown, as is their prognosis. In this case-based review, we report a pediatric patient with SLE complicated with pancreatitis and MAS, and performed a literature review. We report an 11-year-old girl with SLE and MAS who developed pancreatitis on the second day of methylprednisolone pulse therapy (500 mg/day). We continued methylprednisolone pulse therapy, and performed three rounds of DNA-immunoadsorption and three rounds of hemoperfusion. A second course of methylprednisolone pulse therapy was initiated 9 days later. The patient received a monthly cyclophosphamide pulse therapy (10 mg/kg/day, 2 consecutive days every month) for 6 months, after which she was treated with mycophenolate mofetil 20 mg/kg/day. The condition of the patient gradually improved, her blood amylase and lipase decreased. She was in a stable condition during 13-month follow-up period. Review of the literature of pediatric patients with SLE and pancreatitis showed that there are 127 cases that have been reported in the past 30 years, 40 cases were excluded in our study because of inadequate information. Of the 87 patients included in our literature review, the mortality rate was 33.33%, and 52.86% of the patients with pancreatitis had MAS at the same time. Pancreatitis is uncommon in SLE, but must be suspected if a patient with SLE develops digestive symptoms. Patients with SLE with pancreatitis have a high incidence of MAS and high mortality rate; however, early recognition and effective treatment can relieve the disease symptoms.

Keywords Pancreatitis · Lupus erythematosus, systemic · Macrophage activation syndrome · Pediatrics · Case reports

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with various clinical presentations, and virtually every organ and system can be affected. Gastrointestinal symptoms are common in SLE patients, and the incidence of gastrointestinal involvement is 19% in pediatric SLE and 8–40% in adult SLE [1]. Ascites is the most common in abdominal involvement, which occurs in 8–11% of adult patients with SLE [1]. Lupus-related pancreatitis in adults has been reported [2]. The pathogenic mechanism of lupus-related pancreatitis is complex and multifactorial, and might be related to vasculitis and immune-mediated pancreatic

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injury [2]. Acute pancreatitis is very rare in pediatric SLE populations, with most published studies being related to case reports. Some of these patients also suffered from macrophage activation syndrome (MAS) [3]. The number of pediatric patients with lupus pancreatitis is very small; therefore, the mortality and outcome of children with lupus pancreatitis are unknown. The incidence of MAS in pediatric lupus pancreatitis is also unknown.

In the present study, we report an 11-year-old girl with SLE and MAS who developed pancreatitis on the second day of methylprednisolone pulse therapy (500 mg per day for 3 days). The clinical presentation, laboratory profiles, and treatment are described. In presenting this case, along with other similar rare cases in the literature, our aim was to draw the attention of fellow rheumatologists to pancreatitis, which is a rare, but life-threatening, complication of SLE.

Case presentation

On January 30th, 2018, an 11-year-old girl was admitted to our hospital complaining of intermittent fever lasting for 3 weeks, with a maximum body temperature of 39 °C. The fever was accompanied by knee pain, fatigue, and a paroxysmal cough. She was intermittently treated with cephalosporins at a local hospital; however, the symptoms persisted. Her chest X-ray and bone marrow smear were normal. Blood tests in the local hospital showed leukopenia, thrombocytopenia and high serum ferritin (shown in Table 1). Her past history and family history were unremarkable. She was suspected of suffering from hemophagocytic lymphohistiocytosis and transferred to the hematology department of our hospital. On admission, she appeared sick, was febrile (38.0 °C), and had a heart rate of 110 beats/min, a respiratory rate of 22 breaths/min, and her blood pressure was 120/85 mmHg. No abnormal findings were observed in her heart, lungs, and abdomen upon physical examination.

Lung infection was confirmed using chest computed tomography (CT). An abdominal CT showed no abnormality. Her Epstein–Barr virus (EBV)-DNA, cytomegalovirus (CMV)-DNA, *Mycoplasma pneumoniae* antibody, tuberculosis antibody, hepatitis B, hepatitis C, syphilis, HIV, and VB19-DNA tests were negative. She was treated with cefoperazone sulbactam for the lung infection.

The results of the laboratory tests are shown in Table 1.

After the results of the laboratory parameters were obtained, she was diagnosed as having SLE and MAS, and was transferred to our department: The Department of Nephrology and Immunology. Pulse therapy with methylprednisolone was administered (500 mg/day for 3 days). On the second day of pulse treatment, the patient developed abdominal pain and vomiting. A physical examination revealed abdominal tenderness and distention, and abdominal radiography indicated intestinal dilatation and incomplete intestinal obstruction. The patient received an intravenous injection of omeprazole and gastrointestinal decompression; however, her abdominal pain and distention did not improve, and she became lethargic. Abdominal CT demonstrated fluid accumulation surrounding the swollen pancreas. Amylase and lipase were tested immediately, the results confirms pancreatitis. Meropenem to treat the infection and parenteral nutrition support was initiated. Somatostatin was also administrated.

The treatment process is shown in Fig. 1.

Her abdominal pain gradually disappeared and her abdominal distension was relieved in 5–6 days. The laboratory parameters were gradually restored to normal. A kidney biopsy was performed, and most of the glomeruli showed mild to moderate mesangial hyperplasia. Four of the glomeruli had severe segmental mesangial hyperplasia, with a small amount of cellular necrosis and mild fibrosis being discovered in the tubulointerstitium. Oral prednisone (2 mg/kg/day) was administered and then gradually reduced. The patient then received monthly cyclophosphamide pulse therapy (10 mg/kg/day, 2 consecutive days every month) for 6 months. Her urine protein and hematuria became negative after 3 months. The patient was treated with mycophenolate mofetil 20 mg/kg/day after 6 months of cyclophosphamide pulse therapy. The patient remained in a stable condition after 13 months of follow-up.

Search strategy

A literature search for children with SLE and pancreatitis was carried out using various databases (Web of Science, Wiley Online Library, Elsevier Science Direct, and Pubmed) up to January 2019. The search was conducted using following key words: “lupus”, “pancreatitis”, and “child”, “childhood”, “children”, “pediatric”, “juvenile”, and “adolescent”. Studies reporting patients under 18 years old with lupus pancreatitis who were documented in the English language literature over the past 30 years (from 1988 to 2018) were examined.

Literature review

We identified 41 articles describing 127 patients in total [1–41].

Thirteen articles were excluded because of inadequate information [29–41]. Twelve papers reported 40 cases of lupus pancreatitis in children, 13 of whom died; however, details were not provided [29–40]. Another paper

Table 1 Laboratory parameters of the patient with systemic lupus erythematosus and acute pancreatitis and macrophage activation syndrome

Laboratory parameters	One day before admission	Day 1 (January 30th. On admission)	Day 2 (diagnosis of SLE and MAS. Start of MPT)	Day 3 (detection of pancreatitis)	Day 5	Day 7	Day 15	Day 34	Normal range
WBC ($\times 10^9$/L)	2.29	1.4	–	–	8.71	7.82	11.73	7.93	4–10
Neutrophils ($\times 10^9$/L)	1.53	0.74	–	–	7.69	6.59	10.51	6.24	2–7.5
Lymphocytes ($\times 10^9$/L)	0.57	0.46	–	–	0.6	0.57	0.66	1.16	0.8–4
Platelets ($\times 10^9$/L)	78	56	–	–	63	56	114	374	100–300
Hemoglobin (g/L)	96	90	–	–	97	71	80	98	110–140
Fibrinogen (g/L)	–	1.38	–	–	1.32	1.6	1.7	–	2–4
Serum albumin (g/L)	–	27.6	–	–	27	29.8	26.8	39.1	38–54
Triglyceride (mmol/L)	–	2.57	–	–	2.5	2.87	2.3	2.33	0–1.7
ALT (U/L)	–	374	–	–	185.7	135.9	89.4	53.7	5–35
AST (U/L)	–	995.8	–	–	620.3	521.1	259.5	54.3	10–67
Total bilirubin (μmol/L)	–	42.5	–	–	73.56	108.98	78	18.87	3.4–17.1
Direct bilirubin (μmol/L)	–	33.2	–	–	60.32	87.36	62.62	12.52	0–10
serum creatinine (μmol/L)	–	54.9	–	–	57.7	52.7	34.7	37.8	5–84
Amylase (U/L)	–	–	–	438.5	–	433.3	99	184	0–100
Lipase (U/L)	–	45.3	–	1113.1	–	814.9	145	72.2	13.0–63.0
Ferritin (ng/mL)	1364	2115	–	–	1852	1605	687	583	11.00–336.20
Proteinuria	–	50 mg/dL (+)	–	–	Negative	Negative	Negative	Negative	Negative
Hematuria (/μL)	–	52	–	–	314	268	61	28	0–22
24 h urine protein (mg)	–	627	–	–	–	–	–	–	2–119
ANA	–	1:1000	–	–	–	–	–	–	Negative
Anti-dsDNA antibody	–	1:320	–	–	–	–	–	–	Negative
Soluble CD25 (pg/mL)	–	21127	–	–	–	–	–	–	< 6400
NK cell activity	–	12.79%	–	–	–	–	–	–	> 15.11%
IgA (g/L)	–	2.46	–	–	–	–	–	2.62	0.63–1.79
IgG (g/L)	–	14.46	–	–	–	–	–	11.54	6.36–10.04
IgM (g/L)	–	1.01	–	–	–	–	–	1.51	0.29–1.41
C3 (g/L)	–	0.16	–	–	–	–	–	0.75	0.79–1.52
C4 (g/L)	–	0.05	–	–	–	–	–	0.14	0.16–0.38

WBC white blood cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ANA* anti-nuclear antibody, *dsDNA* double-stranded DNA, *NK cell* natural killer cell, *C3* complement component 3, *C4* complement component 4, *SLE* systemic lupus erythematosus, *MAS* macrophage activation syndrome, *MPT* methylprednisolone pulse therapy

reported 13 cases of childhood-onset SLE [41]; however, the number of patients with pancreatitis before the age of 18 years was not stated, and the study was from the same hospital as another report [37] and the time of the two articles overlapped. Thus, we could not exclude the possibility that patients were recruited repeatedly; therefore, this article was excluded.

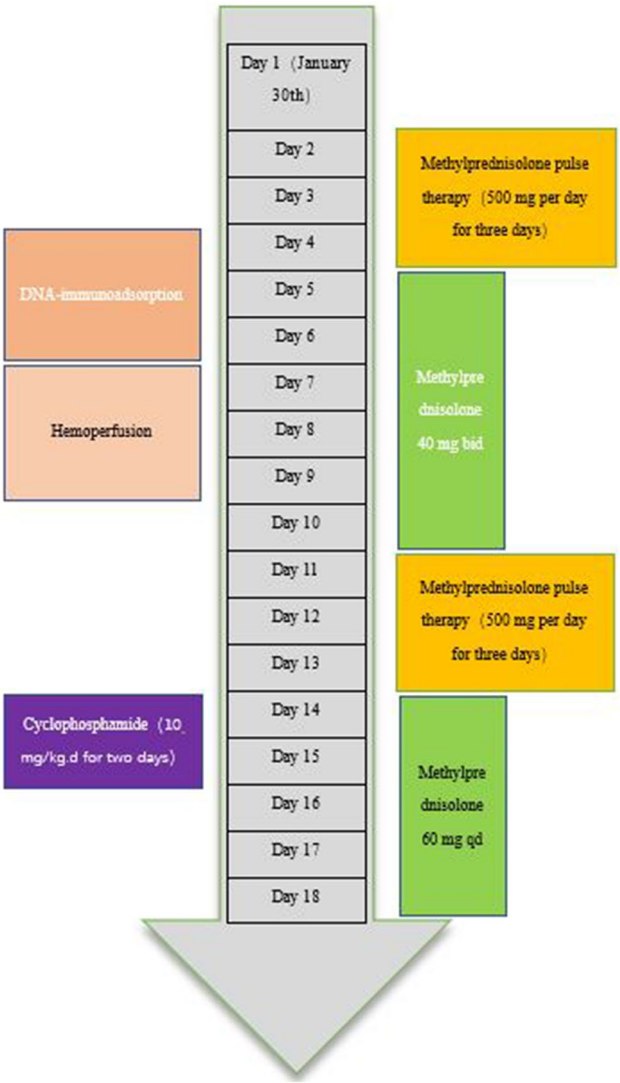

Fig. 1 Timeline of interventions in the pediatric systemic lupus erythematosus patient with pancreatitis and macrophage activation syndrome

Ultimately, 28 articles were included in our study, comprising 21 case reports and 7 original articles. Altogether 87 patients were analyzed [1–28].

Five pediatric patients were reported from 1988 to 1998; 18 from 1999 to 2008, and 64 from 2009 to 2018. In total, 29 patients died, giving a mortality rate of 33.33%. It is not clear wether MAS existed in 17 patients because of inadequate descriptions, of the 70 children with adequate information, 37 could be diagnosed as having MAS, as shown in Table 2.

Discussion

Pancreatitis is rare in pediatric SLE patients, and there were only 127 pediatric patients reported in the past 30 years in English literature as far as we know. The past 30 years have witnessed an increase in the number of pediatric patients reported as having SLE with pancreatitis, more cases may be discovered in the future. Although it is rare, the mortality rate is high. Of the 87 patients included in our literature review, the mortality rate was 33.33%, some survivors had pancreatic pseudocyst or diabetes mellitus. These findings are consistent with the literature [42].

52.86% (37/70) of the patients with pancreatitis in our review had MAS at the same time, the frequency is much higher than those patients without pancreatitis, which is about 16–20% [43]. The occurrence of pancreatitis and MAS in SLE may not be an accident. A study from Brazil showed that 85% of children with lupus pancreatitis suffered from concurrent MAS [19]. According to Campos et al., the pancreas may be a target organ of MAS in patients with SLE [3].

Gastrointestinal involvement in patients with SLE is a challenging from a diagnostic perspective, the symptoms include anorexia, nausea, vomiting, and abdominal pain [44]. These symptoms can be caused by many factors, some of these complications can be life threatening, such as perforation, intestinal infarction, and pancreatitis [42, 44].

The incidence of pancreatitis in adult patients with SLE varies from 0.7 to 4% [3]. There has been no large sample-sized survey of the incidence of pancreatitis in children with SLE. A survey from France showed that pancreatitis is the second most common gastrointestinal symptom in SLE [1]; however, pancreatitis is rarely reported in children. An explanation might be as follows: Many patients with SLE with abdominal pain may be diagnosed as gastritis or other diseases; therefore, pancreatic enzymes do not get measured, and mild pancreatitis clears up by itself or is relieved by the corticosteroids administered to treat SLE [18]. Thus, the incidence of pancreatitis in SLE might be underestimated [18].

The diagnosis of pancreatitis in SLE is not difficult, and is mainly based on clinical symptoms, abdominal CT, and elevated serum levels of amylase or lipase. However, the etiology of pancreatitis is complex. Some scholars believe that pancreatitis in lupus may be related to the use of glucocorticoids [20]. Current oral glucocorticoid use may be associated with an increased risk of acute pancreatitis; the risk is highest at 4–14 days after drug dispensation and is attenuated thereafter [45]. Methylprednisolone pulse therapy may also be related to pancreatitis. At least nine cases of pancreatitis after methylprednisolone pulse

Table 2 Review of pediatric systemic lupus erythematosus cases associated with pancreatitis

Year, author	Country	No. of cases	Age (years)/gender	Time interval between SLE diagnosis and detection of pancreatitis	MAS	Treatment after the first episode of pancreatitis	Outcome
1988, Rupprecht et al. (abstract in English) [4]	Germany	1	17, F	6 years before SLE	NA	NA	Improved
1991, Montes de Oca et al. [5]	France	1	14.3, M	NA	NA	NA	Death
1992, Garcia-Consuegra et al. [6]	Spain	1	15, F	9 months after SLE	Yes	Prednisone 100 mg/day	Improved, pancreatic pseudocyst
1994, Huang et al. [7]	China	1	13, F	Simultaneous	No	Oral prednisolone 2 mg/kg/day	Improved
1995, Kolk et al. [8]	Germany	1	16, F	3 years after SLE	NA	NA	Death
2002, Al-Mayouf et al. [9]	Saudi Arabia	1	13, F	9 years after SLE	No	Intravenous MP, then changed to prednisone 1 mg/kg/day	Improved, pancreatic pseudocyst
2002, Ramanan et al. [10]	United Kingdom	1	14, F	1 month after SLE (after MP pulse therapy)	Yes	MP pulse therapy, hemodialysis, plasmapheresis	Death
2003, Penalva et al. [11]	Spain	1	14, F	5 years after SLE	No	Prednisone, splenopancreatectomy	Improved, small pseudocysts
2003, Fan et al. [12]	China	1	12, F	1 year after SLE	No	Intravenous MP 45 mg/day	Improved
2005, Cosentini et al. [13]	Italy	1	16, NA	NA	NA	NA	Death
2006, Perrin et al. [14]	France	1	13, F	Simultaneous	No	MP pulse therapy, then prednisone 1.5 mg/kg/day	Improved
2007, Richer et al. [1]	France	12	NA	8 patients with pancreatitis at the onset of SLE, 4 patient after the diagnosis of SLE	One patient had MAS	Starting GC or increasing the dosage of GC	Improved
2009, Rose et al. [15]	India	1	14, F	Simultaneous	NA	MP pulse therapy	Improved, stabilized in 8 months, then died (no detailed information)
2010, Tominaga et al. [16]	Japan	1	12, F	Within 1 month after SLE	Yes	Plasmapheresis, MP pulse therapy, CTX pulse therapy	Improved

Table 2 (continued)

Year, author	Country	No. of cases	Age (years)/gender	Time interval between SLE diagnosis and detection of pancreatitis	MAS	Treatment after the first episode of pancreatitis	Outcome
2010, Campos et al. [3]	Brazil	11	11.5 (8.8–17.9), 10 F, 1 M	0 (5 months before–57 months after) months, 4 patients had pancreatitis at the onset of SLE	10 patients had MAS	Intravenous methylprednisolone/IVIG/MMF/intravenous cyclophosphamide	4 patients died, 2 patients had diabetes mellitus after AP
2011, Al-Musawi et al. [17]	Kingdom of Bahrain	1	12, M	5 months before SLE, and several pancreatitis attacks occurred in subsequent years	No	Oral GC + CTX pulse therapy + hydroxychloroquine, intermittent MP pulse therapy, rituximab	Improved
2012, Yang et al. [2]	China	5	14 (14–16), gender information not available	2 (1–3) years after SLE	NA	GC	4 patients died
2013, Limwattana et al. [18]	Thailand	2	9 (7–11), F	2 days after prednisone was given 2 mg/kg/day for the treatment of SLE/3 days after prednisone was given 2 mg/kg/day for the treatment of SLE.	NA	MP pulse therapy/continue oral prednisone	Improved
2016, Gormezano et al. [19]	Brazil	12 patients with 13 episodes	13.57 ± 0.75, 11 F, 1 M	8 (5–88) months after SLE	there were 13 episodes,11 episodes with MAS	Intravenous MP, intravenous immunoglobulin, CTX	4 patients died, 2 patients had diabetes mellitus after AP
2016, Marques et al. [20]	Brazil	22	15 (9–20), 20 F, 2 M	0.6 (0–10) years,6 patients had pancreatitis at the onset of SLE	8 patients had MAS	GC/antimalarials/immunosuppressive agents/IVIG	7 patients died
2016, Basturk et al. [21]	Turkey	1	3, F	Pancreatitis occurs before MP treatment after the diagnosis of SLE	Yes	Intravenous MP 2 mg/kg/day + azathioprine	Improved
2017, Marija et al. [22]	Serbia	1	14, F	Simultaneous	Yes	Intravenous MP 2 mg/kg/day + IVIG	Death
2017, Manjusha et al. [23]	India	1	17, F	2 years after SLE	NA	MP 100 mg twice a day	Death
2018, Parasher et al. [24]	India	1	12, F	Simultaneous	Yes	MP pulse therapy 30 mg/kg/day and then oral GC	Improved

Table 2 (continued)

Year, author	Country	No. of cases	Age (years)/gender	Time interval between SLE diagnosis and detection of pancreatitis	MAS	Treatment after the first episode of pancreatitis	Outcome
2018, Jiang et al. [25]	China	1	11, F	Simultaneous	NA	MP pulse therapy 10 mg/kg/day and then oral GC	Improved
2018, Qadiry et al. [26]	Morocco	2	Both 14, F	Simultaneous	NA	GC + CTX	Both of them died
2018, Loulouga et al. [27]	Morocco	1	14, F	11 months after SLE	Yes	Hydroxychloroquine + prednisone 15 mg/day	Death
2018, Aanchal et al. [28]	China	1	11, F	1 day after prednisone was given when SLE was diagnosed	NA	Intravenous MP therapy, CRRT	Improved

M male, *F* female, *MP* methylprednisolone, *SLE* systemic lupus erythematosus, *MAS* macrophage activation syndrome, *IVIG* intravenous immunoglobulin, *MMF* mycophenolate mofetil, *CTX* cyclophosphamide, *CRRT* continuous renal replacement therapy, *GC* glucocorticoid, *CSA* cyclosporin A, *AP* acute pancreatitis, *NA* not available

therapy have been reported, with a median latent period of 5 days [46]. However, only one pediatric patient with SLE who developed pancreatitis after methylprednisolone pulse therapy has been reported in the literature [10].

Our case developed pancreatitis on the second day of methylprednisolone pulse therapy; however, it was difficult to determine whether the pancreatitis was caused by the disease or by the glucocorticoids. We believe that in our case, the pancreatitis was possibly caused by lupus itself rather than glucocorticoids, for the following reasons: (1) some patients with SLE could develop pancreatitis before, or in the absence of, the use of corticosteroids [12, 18, 21]; (2) Patients with pancreatitis tend to achieve symptom resolution using continuous glucocorticoids or increasing the dose of glucocorticoids [1, 18]. (3) The occurrence of pancreatitis is related to the disease activity of lupus: the SLE disease activity index was significantly higher in patients with pancreatitis than in those without [1, 20]; and (4) we started extracorporeal blood purification and continued methylprednisolone pulse therapy after our patient developed pancreatitis, and her condition gradually improved. A second course of methylprednisolone pulse therapy 9 days later did not induce pancreatitis. Increasing evidence suggests that the occurrence of pancreatitis in patients with SLE is not related to glucocorticoids. Among the patients who received intensive glucocorticosteroids, immunosuppressive agents, or both, 75% exhibited a favorable prognosis [2], indicating that these treatments could improve the survival rate of patients with SLE and pancreatitis [1, 2].

As a method to rapidly and selectively eliminate autoantibodies and immune complexes in patients with SLE, DNA-immunoadsorption therapy can significantly reduce disease activity and protect organ function. For patients with severe SLE, immunosuppressive therapy combined with DNA-immunoadsorption may improve their prognosis, thereby saving their lives [47, 48]. Our patient was treated with DNA-immunoadsorption and glucocorticosteroid pulse therapy simultaneously, after which her clinical symptoms gradually eased. However, it was not possible to dissect the therapeutic effect of DNA-immunoadsorption from that of the corticosteroids.

The prognosis of lupus-related pancreatitis is not good, the mortality rate could be as high as 45%, 22% of patients with lupus-related pancreatitis may experience recurrent pancreatitis attacks, and 12% of patients develop pancreatic pseudocysts [42].

Although pancreatitis in SLE is rare, it could be life threatening, physicians should be suspicious of pediatric patients with SLE who present with gastrointestinal involvement. Pancreatitis and MAS often occur simultaneously in pediatric patients with SLE, and mortality is high. However, early recognition and effective treatment can relieve the disease symptoms.

Author contributions QL/MZ: writing of initial draft of manuscript, editing and revision of manuscript at all stages of its production, review of the literature and management of the patient. HT/YS/YZ: contributed to editing of manuscript, review of the literature and management of the patient. QX: critically revised the manuscript, review of the literature and management of the patient. XL: critically revised the manuscript at all stages of its production, final approval of manuscript, review of the literature and management of the patient.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical standards The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of our hospital.

Informed consent Informed consent was obtained from our patient and her parents.

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