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Case Report

A rare presentation of rapidly progressing myopathy in an adolescent

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ABSTRACT

We present a case of severe juvenile dermatomyositis with limited response to steroids in an adolescent who developed symptoms within hours after receiving Pfizer BNT162b2 coronavirus disease 2019 vaccine. The patient presented with severe weakness of proximal muscles, dyspnoea, and tachycardia. His muscle enzymes were raised, and he was diagnosed with severe juvenile dermatomyositis following magnetic resonance imaging and muscle biopsy. His management was challenging, requiring multidisciplinary input, and difficult decisions with regard to the appropriate immunomodulatory treatments. The patient had to undergo escalating immunosuppressive treatments before he began to recover clinically and biochemically. To our knowledge, this is the first case in an adolescent although a few cases of similar presentations following coronavirus disease 2019 vaccination have been reported in adults. Elucidating the potential relationship of the vaccine with this severe myopathy in an adolescent is important for global vaccination policies, but avoiding the conflation of association with causation is also crucial in the context of the pandemic.

KEYWORDS: Juvenile dermatomyositis; myopathy; COVID-19 vaccine; Pfizer vaccine; case report

Introduction

During the ongoing coronavirus disease 2019 (COVID-19) pandemic, vaccination proved to be the most effective intervention dramatically reducing severe morbidity and death with >4.9 billion people vaccinated to date [1].

These vaccinations elicit a robust humoral response and have been shown to be safe and effective in the majority of the vaccinated populations. Common side effects include fatigue and myalgia surrounding the injection site and, only rarely, more severe adverse events [2].

An increase in new-onset autoimmune phenomena post COVID-19 vaccination has been reported; it is a known, rare, side effect associated with other vaccines as well [3].

We report a case of severe juvenile dermatomyositis (JDM) in an adolescent that may have been related to COVID-19 vaccination.

JDM is a rare childhood myopathy characterised by proximal muscle weakness, muscle inflammation, and cutaneous manifestations. Autoantibodies are detected in the majority of cases of this putatively autoimmune disease [4].

Case presentation

A 16-year-old male of British and East-Asian descent presented to our hospital's emergency department with marked weakness of neck flexion and extension; proximal upper and lower limbs; and back pain, palpitations, dyspnoea on exertion, nasal regurgitation, and dysphagia. He also had associated fatigue, reduced appetite, and reported slight weight loss. His weight was 74.5 kg on admission, with body surface area of 1.99 m^2 using the Du Bois formula [5]. The weakness developed within ~3 hours of receiving the second Pfizer COVID-19 vaccine dose when he noticed unusual weakness during an after-school sports activity. He deteriorated dramatically over the following few weeks prior to presentation. He was unable to dress himself due to weakness and was dyspnoeic on the slightest exertion such as mobilising to the bathroom.

He experienced mild bilateral shoulder and back pain for around 2 months prior to the second vaccination. He had his first dose of the vaccine 3 months prior to admission with no significant side effects other than mild fatigue and myalgia surrounding the injection site.

He is a lone twin from a 2-month premature delivery. He was a non-drinker, non-smoker, fit, and healthy school pupil. His past medical history was unremarkable with no regular medications and no trips abroad or camping in the 2 years prior to presentation.

On presentation, the patient could not be examined sitting up due to significant back pain and weakness. He had a slight waddling gait and was persistently tachycardic. Physical examination revealed marked proximal weakness with 3/5 strength on Medical Research Council scale in shoulder

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abduction and hip flexion bilaterally, mild weakness in elbows and knees bilaterally (4/5 for flexion and extension), and normal strength in wrists and ankles bilaterally (5/5 in all movements).

All reflexes were present and symmetrical. Sensory testing was normal throughout.

Nailfold capillaroscopy revealed marginal dilatation with haemorrhages (Figure 1).

Total serum creatine kinase, C-reactive protein, alanine transaminase, aspartate aminotransferase, and lactate dehydrogenase were raised. Platelet count and serum albumin were reduced (Table1).

Other blood results were normal.

Further extensive investigations including thyroid function, erythrocyte sedimentation rate, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase antibody, liver ultrasound, respiratory function tests, echocardiogram, and ophthalmology review were all normal. Computed tomography chest/abdomen/pelvis showed no evidence of malignancy. Despite persistent tachycardia and dyspnoea on exertion, computed tomography pulmonary angiogram was normal.

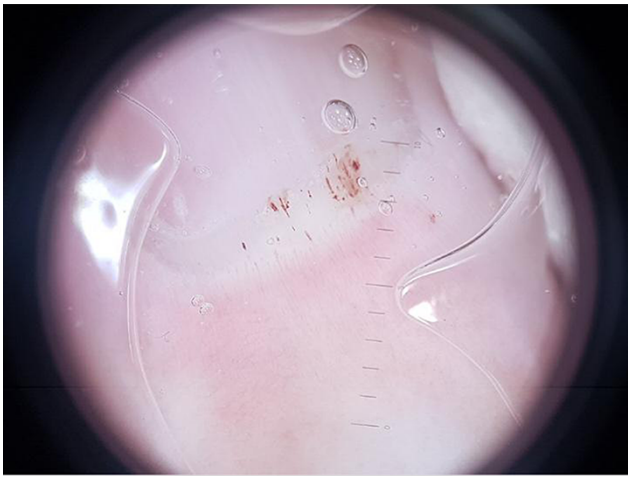

Figure 1. Nailfold capillaroscopy showing nailfold haemorrhages.

Table 1. Laboratory findings at admission and discharge.

Relevant laboratory findings	Admission	Discharge	Normal range
C-reactive protein	**7**	<4	0–6 mg/l
White blood cells	6.5	5.4	4.2–10.8 × 10^9/l
Neutrophils	5.3	3.2	1.7–7.9 × 10^9/l
Platelets	**141**	203	160–385 × 10^9/l
Haemoglobin	160	**116**	130–166 g/l
Creatine kinase	**5978**	**24**	40–320 U/l
Creatinine	**50**	**43**	62–115 μmol/l
AST	**192**	NA	0–34 U/l
ALT	**346**	38	10–49 U/l
LDH	**875**	249	215–368 U/l
D-dimer	**992**	255	<500 ng/ml FEU
Ferritin	**2473**	NA	25–350 ng/ml
NT-proBNP	22	NA	<400 pg/ml

Abnormal findings are in bold.
ALT: alanine transaminase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; FEU: fibrinogen equivalent units; NT-proBNP: N-terminal pro B-type natriuretic peptide.

Viruses (including hepatitis B, hepatitis C, HIV, and COVID-19), illicit drugs, and other toxins were excluded.

Magnetic resonance imaging of his thighs showed marked oedema in the anterior compartment (Figure 2), in keeping with extensive myositis.

Nerve conduction studies were performed on both upper and lower limbs. The results revealed normal sensory and motor responses over the right radial, median, tibial, and sural nerves. F waves of the right median nerve (abductor pollicis brevis) and right tibial nerve (abductor hallucis) showed normal minimum latency. Repetitive stimulation over the abductor pollicis brevis and right trapezius revealed no significant decrement.

Electromyography over the proximal and distal muscles of the upper and lower limbs revealed occasional small polyphasic units in proximal muscles amongst larger recruiting ones, with infrequent spontaneous features in the left deltoid. Moreover, the clinically weak proximal muscles including quadriceps femori and deltoids revealed a full pattern of recruitment suggestive of a myopathic process.

The clinical presentation of proximal muscle weakness, intact reflexes, and sensation, with elevated serum muscle enzymes and some spontaneous features on electromyography, was suggestive of an inflammatory myopathy.

Left quadriceps femoris muscle biopsy showed a pauci-inflammatory necrotising myopathy (Figure 3). Hematoxylin and eosin-stained sections showed perifascicular fibrosis and inconspicuous chronic inflammation at lower magnification (Figure 4) and subtle perifascicular/septal atrophy with basophilic fibres at higher magnification (Figure 5). Electron microscopy revealed endothelial tubuloreticular inclusions on electron microscopy (Figure 6). There was no evidence of mitochondrial myopathy, neurogenic atrophy, muscular dystrophy, selective fast fibre atrophy, or vasculitis.

Hep2 anti-nuclear antibody assay [using the NOVA Lite HEp-2 IgG (FC Specific) kit provided by Werfen with 1:80 dilution] showed a multiple nuclear dot and homogeneous staining pattern, indicating the presence of an autoantibody. We therefore performed a connective tissue disease (CTD) screen [using fluorescence enzyme immunoassay, with the Phadia 'EliA CTD Screen' kit provided by Thermo Fisher Scientific with 1:10 dilution]. This assay covers 17 different antigens commonly found in CTDs; however, our patient tested negative for this assay. We then used the

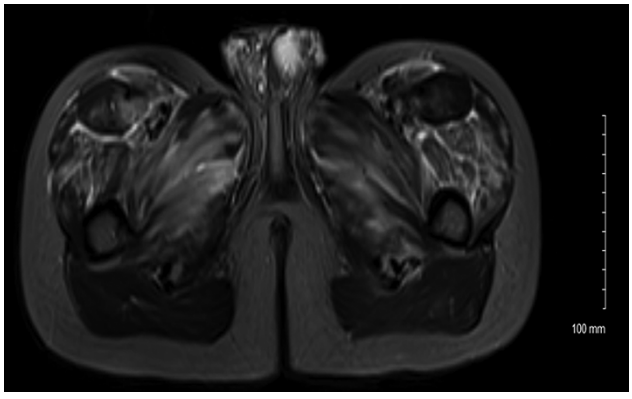

Figure 2. Magnetic resonance imaging (MRI) of thigh showing extensive oedema in anterior thigh compartment on T2-weighted imaging.

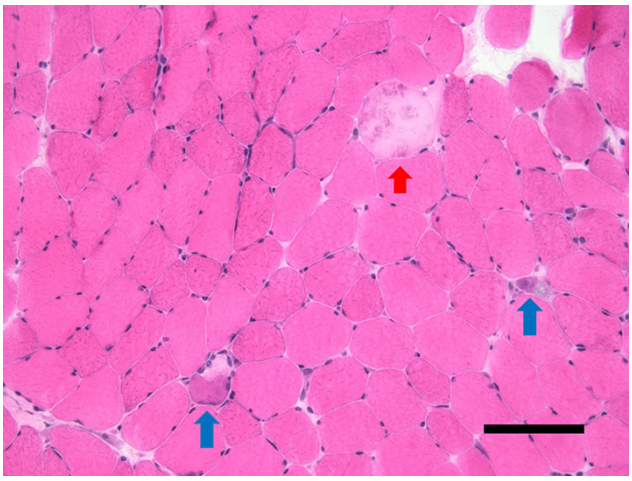

Figure 3. Left quadriceps femoris muscle biopsy Hematoxylin and eosin (H&E). Upper arrow: necrotising muscle fibre. Lower arrows: regenerating muscle fibre. Bar for scale = 100 μm.

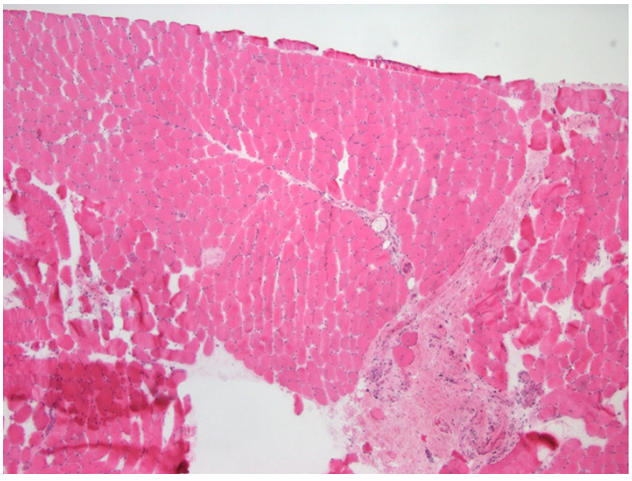

Figure 4. H&E-stained section showing perifascicular fibrosis and inconspicuous chronic inflammation at lower magnification (×50).

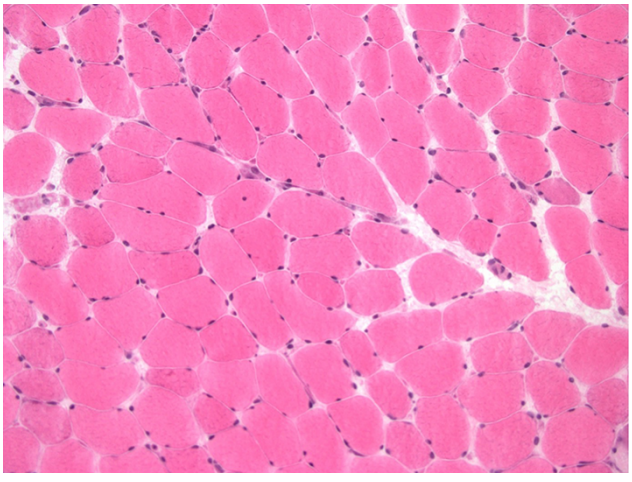

Figure 5. H&E-stained section showing subtle perifascicular/septal atrophy with basophilic fibres (magnification ×200).

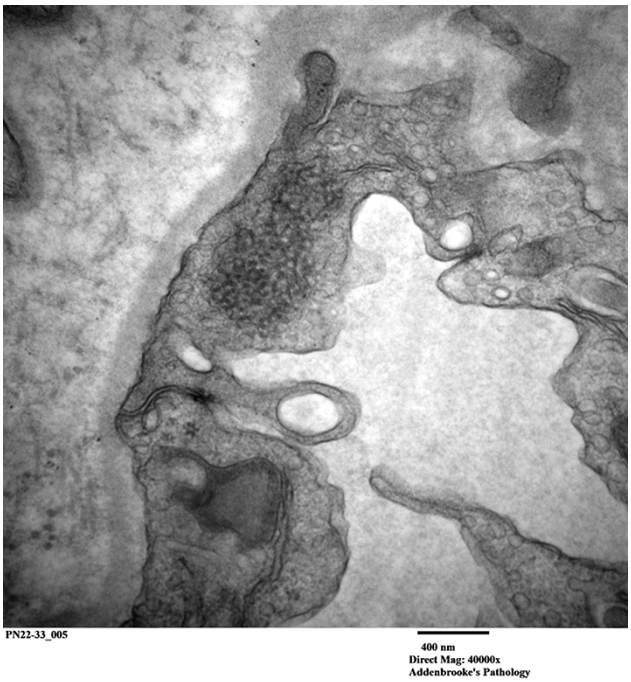

Figure 6. Endothelial tubuloreticular inclusions (Electron microscopy 40,000×).

myositis antibody extended panel (using the immunoblot kit 'EUROLINE Autoimmune Inflammatory Myopathies 16Ag (IgG)' provided by Euroimmun with 1:101 dilution). The strips are coated with the following purified antigens: Mi-2α, Mi-2β, TIF1Y, MDA5, nuclear matrix protein (NXP)2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, and Ro-52. This test returned positive for an important myositis-specific antibody, particularly in JDM, anti-NXP2 autoantibodies [6, 7].

This result is consistent with the multiple nuclear dot pattern seen on the Hep2 slides (AC-6 according to the International Consensus of ANA Patterns) [8].

On admission, the patient was started on a 3-day course of pulse dose (1 g) intravenous methylprednisolone. On Day 3 of admission, he was switched to oral prednisolone (60 mg). There was an initial clinical and biochemical improvement with improved strength and decreasing creatine kinase (CK) (dropping from ∼6000 U/l initially to ∼2000 U/l on Day 8). However, this improvement was not sustained. On Day 8 of admission, CK rose again with worsening weakness, dyspnoea, and dysphagia, leading to the decision to administer intravenous immunoglobulins (IVIgs) on Day 15 of admission. The patient received 140 g of IVIg over 5 days.

There was no significant benefit within 7 days of IVIg treatment, with CK continuing to rise, and further deterioration of dyspnoea and dysphagia eventually requiring nasogastric tube insertion 21 days after admission. On Day 23, mycophenolate mofetil (MMF) was started as well, gradually titrated up to 1 g twice a day. Due to continued clinical and biochemical deterioration, despite these interventions, plasma exchange (PLEX) was initiated on Day 25 of admission and was administered over 5 days.

On Day 27, within 2 days of PLEX administration, clinical improvement was noted. Cyclophosphamide (two doses

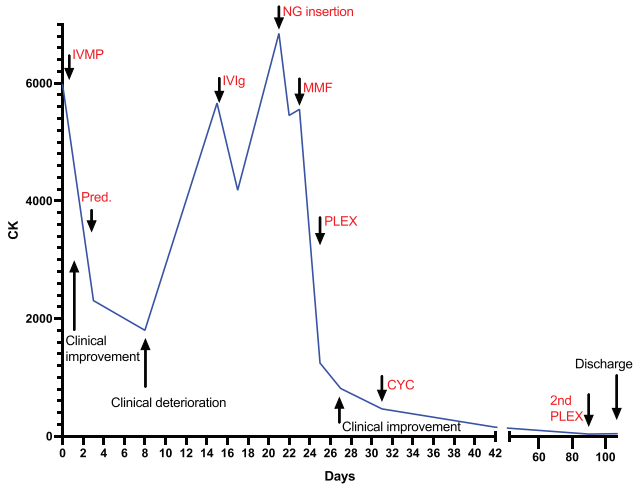

Figure 7. Disease course and corresponding creatine kinase (CK) levels throughout admission. IVMP: intravenous methylprednisolone, Pred.: prednisolone, CYC: cyclophosphamide.

of 1000 mg followed by four doses of 800 mg) was started on Day 31 following sperm collection. CK gradually decreased, eventually returning to normal range (239, normal: <320 U/L) on Day 42 of admission. This improvement was sustained on intravenous methylprednisolone and was followed by a reduced regimen of prednisolone (13 mg), MMF (250 mg), and cyclophosphamide (800 mg).

Due to persistently low lymphocyte count post MMF initiation (<1, normal range: 1.20–5.00 10^9/l), MMF was discontinued. Symptomatic dysphagia persisted, not improving at the same rate as his general strength and biochemical markers. Thus, he underwent a second course of PLEX 3 months after the initial presentation, after which his swallow and mobility improved significantly.

On Day 17 of admission, the patient noticed a bright red rectal bleeding, but flexible sigmoidoscopy demonstrated haemorrhoids and the bleeding settled without intervention.

Following 107 days of hospitalisation, 73 of which he had to be fed via a nasogastric tube due to high aspiration risk, the patient was discharged, mobilising independently on a weaning dose of oral prednisolone (22.5 mg) to be continued and reviewed in rheumatology follow-up clinics.

Throughout the course of the illness, CK measurements closely correlated with the patient's clinical presentation (Figure 7).

Anti-NXP2-positive dermatomyositis is associated with an increased risk of developing malignancy in adults [9, 10]. To our knowledge, there are no reports of an association between malignancy and JDM specifically. However, given the age of our patient (16 years old), it may be prudent to monitor the patient for malignancy in the future.

Discussion

This is a case of an adolescent presenting with a severe myopathy with limited response to steroids, in which symptom onset occurred hours after COVID-19 vaccination. While it is essential to detect the possible vaccine side effects, it is important to avoid the serious, yet common, post hoc ergo propter hoc fallacy when interpreting these reports.

The exact diagnosis of this myopathy was challenging, as several findings in this patient were inconclusive, some suggesting the diagnosis of JDM, while others pointing towards 'dermatomyositis sine dermatitis'.

The histopathological diagnosis of pauci-inflammatory immune-mediated necrotising myopathy (Figure 3) is consistent with an immune-mediated necrotising myopathy or necrotising autoimmune myopathy, a broad diagnostic category including systemic lupus erythematosus, and antibody-related myopathies associated with anti-SRP, anti-Jo1, or anti-HMG-CoA reductase (with or without statin exposure).

The findings of a necrotising process on light microscopy of the muscle biopsy and the presence of endothelial tubuloreticular inclusions within several intramuscular capillaries on electron microscopy (Figures 4, 5, and 6) are consistent with interferon (IFN) activation. This is typical, but not pathognomonic, of JDM [11].

The nailfold abnormalities were in keeping with dermatomyositis despite the absence of typical heliotrope rash.

The diagnosis of JDM was challenged by the lack of characteristic heliotrope rash, Gottron's papules/Gottron's sign, and of typical muscle biopsy features of perivascular chronic inflammation and perifascicular atrophy (although subtle perifascicular atrophy was present on high magnification (Figure 5). These features raise the questions of 'juvenile myositis other than JDM' according to EULAR/ACR classification criteria [12] or 'dermatomyositis sine dermatitis' rather than classical JDM [13]. However, we diagnosed this patient with JDM due to the characteristic muscle ultrastructure, subtle perifascicular atrophy (Figure 6), the presence of anti-NXP2 antibodies (considered to be dermatomyositis-specific antibodies [13]), and the presence of nailfold capillary changes consistent with the skin component of this disease (notwithstanding the absence of the classical skin manifestation).

With regard to the preceding COVID-19 vaccination, there seems to be a link between COVID-19 and myopathies with a proportion of patients with COVID-19 developing various myopathic manifestations, including new-onset inflammatory myopathy, with some testing positive for anti-NXP-2 antibodies, and a number of reported cases of dermatomyositis post COVID-19 infection/vaccination [14, 15].

As of 27 July 2022, the UK Yellow Flag system reports 54 cases of myositis, 14 of dermatomyositis, and 2 cases of immune-mediated myositis post Pfizer vaccine.

A recent systematic review of the literature identified 17 cases of COVID-19 infection-/vaccination-associated dermatomyositis. Dermatomyositis onset post vaccination occurred in seven patients, with the mean age of 59.2 years, and 71.4% of patients were female [15]. However, to our knowledge, our case is the first reported case of COVID-19 vaccination-associated dermatomyositis in an adolescent.

The new onset of autoimmune phenomena has been previously reported with other vaccines. In the vaccine against human papilloma virus, molecular mimicry, the production of autoantibodies, and the role of certain vaccine adjuvants have been proposed as possible mechanisms contributing to the onset of autoimmune diseases post-vaccination [16].

The likely mechanism underlying new-onset dermatomyositis following COVID-19 infection/vaccination is autoimmunity driven by IFN signalling and hyperinflammation, resulting in autoantibody induction.

Interestingly, all reported cases of dermatomyositis post COVID-19 vaccination occurred following the administration of messenger ribonucleic acid (mRNA) vaccines. A possible explanation for this observation is the induction of a strong IFN type I response known to occur with mRNA vaccines [17], which may result in dermatomyositis, a known IFN-driven disease [18]. With regard to NXP-2 specifically, it is known to play an important role in RNA metabolism [19] and that might explain the production of anti-NXP-2 antibodies following vaccination with mRNA vaccines.

In our case, and in three other cases reported in the literature [20–22], the disease onset only occurred after the second vaccine dose, and the reason for this is unclear; a possible explanation may be that the broader spectrum of immune-reactive clones following the second vaccine dose increases the likelihood of autoreactive damaging clones.

Further research is still required to elucidate the exact pathogenic mechanism underlying the potential link between autoimmune diseases and vaccinations in general and the link between dermatomyositis and mRNA vaccinations in particular.

The management of this case posed various challenges to the managing team. He was hospitalised in a neurology ward and was under neurologists' care with regular rheumatological, cardiological, and dermatological inputs from both the paediatric and adult specialists. The various specialties worked together in a multidisciplinary fashion to manage this patient appropriately. On discharge, he continues to be under follow-up of a consultant rheumatologist.

Choosing the right immunomodulatory treatment presented another challenge. The standard therapy, outlined by the British Society for Rheumatology guideline, includes high-dose glucocorticoids as first-line treatment and IVIg, cyclophosphamide, and MMF as second-line treatment options [23]. However, in this case, the patient did not demonstrate sufficient benefits on these therapies and required treatment with PLEX which was previously demonstrated to be an effective 'rescue therapy' in acute dermatomyositis [24].

The possible relationship of this severe, steroid non-responsive JDM to the preceding mild musculoskeletal complaints and/or COVID-19 vaccination is intriguing but unclear. It is important to note that when vaccinating the majority of the population, rare diseases may manifest following the vaccination. Despite the apparent temporal relationship, in our case and other reports, they may or may not be related.

The significant benefit from mass vaccination has to be taken into account, and it significantly reduces morbidity and mortality from COVID-19 and protects the population from associated complications, among which are several autoimmune diseases.

Conflict of interest

None declared.

Funding

None declared.

Patient consent

Both patient and guardian signed consent form for publication.

Ethical statement

Not applicable.

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