Case Report

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Unmasking the Masquerade: A Challenging Case of Systemic JIA with Macrophage Activation Syndrome

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1. Abstract

1.1. Background: This report sheds light on a challenging diagnosis of Systemic Juvenile Idiopathic Arthritis (sJIA) with Macrophage Activation Syndrome (MAS), illustrating the diagnostic hurdles encountered due to misdiagnosis and subsequently inappropriate treatment, which resulted in symptoms masquerading the underlying diagnosis. Its novelty lies in the extensive diagnostic pathway navigated to differentiate it from other potential diagnoses through thorough laboratory and radiological evaluations, emphasizing sJIA's nature as a diagnosis of exclusion.

1.2. Case Presentation: A 15-year-old female patient presented with persistent fever, arthritis, evolving rash, and was eventually diagnosed with MAS, complicating sJIA. Her clinical journey spanned over three years of misdiagnoses and inappropriate treatments, including anti-tuberculous therapy (ATT) and corticosteroids, which led to hepatotoxicity. The diagnosis was reached through comprehensive assessments, including blood tests, radiological imaging, ENA profile and bone marrow studies, ruling out other differential diagnoses and confirming MAS secondary to sJIA.

1.3. Conclusions: This case highlights the critical importance of considering sJIA with MAS in patients presenting with persistent fever and arthritis, amidst a complex clinical picture. It elaborates the necessity for a multidisciplinary approach in diagnosis and the prompt initiation of targeted treatments to mitigate the risks associated with this severe complication. The report also calls for awareness and diagnostic precision in distinguishing sJIA with MAS from other mimicking conditions, thereby contributing to better clinical outcomes.

2. Keywords: Systemic Juvenile Idiopathic Arthritis, Macrophage Activation Syndrome, Misdiagnoses, Autoinflammatory disorders, Hemophagocytic lymphohistiocytosis

3. Introduction

Systemic juvenile idiopathic arthritis (sJIA), historically referred systemic-onset juvenile rheumatoid arthritis (JRA), represents a distinct category within juvenile idiopathic arthritis (JIA) spectra, accounting for approximately 10 to 20 percent of all cases of JIA. Despite its classification under JIA, its pathophysiology aligns more closely with an autoinflammatory disorder, sharing similarities with adult-onset Still's disease (AOSD) when it manifests in individuals aged 16 years or older [1].

In managing sJIA, rigorous oversight is essential due to its systemic nature, which frequently involves serious complications such as infections, macrophage activation syndrome (MAS), and pericarditis, contributing to increased morbidity and mortality [2]. Moreover, less prevalent yet escalating occurrences of chronic lung disease and other internal organ involvements present additional challenges [3,4,5].

The variability in the clinical presentation of sJIA has led to the hypothesis that it may not be a singular disease entity. Its onset is characterized by several months of quotidian pattern fevers and rash, accompanied by arthralgia and arthritis of varying intensities. While some children might experience a transient phase of systemic symptoms, others endure persistently active systemic disease, which is correlated with poorer prognoses [3,6]. The disease can follow monophasic, polycyclic, or persistent patterns, although precise proportions of these patterns in sJIA patients remain unclear due to variability in research studies [6,7,8].

The clinical course of sJIA is unpredictable. Some patients have a monophasic journey where active disease subsides without recurrence after a few months. Others experience a polycyclic course with alternating periods of activity and inactivity, or a persistent course, which may manifest solely as systemic symptoms or evolve into progressive arthritis, sometimes necessitating early joint replacement [6,7,8,9,10,11].

Notably, sJIA can debut at any age, with a peak incidence between one and five years. Delays in diagnosis are not uncommon, particularly when initial symptoms are atypical [5]. At presentation, children may exhibit a range of joint and extra-articular symptoms, including high quotidian fevers and a distinctive salmon-pink rash. Such symptoms often lead to an urgent medical evaluation [4]. Moreover, the potential development of MAS, a severe and life-threatening complication of sJIA, highlights the necessity for swift and accurate diagnosis [6,7].

The case presented here is emblematic of the challenges associated with diagnosing and managing sJIA. This 15-year-old patient's symptoms, including persistent fever, arthritis, and evolving rash, alongside the development of MAS, required a high degree of clinical acumen and a maticulous diagnostic approach. The exclusion of other differential diagnoses such as SLE, latent tuberculosis, and malignancies through extensive laboratory and radiological evaluations, exemplifies the intricate nature of sJIA as a diagnosis

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of exclusion

4. Case Presentation

The patient's clinical symptoms began three years ago when she developed arthralgia and arthritis, involving both small and large joints, accompanied by morning stiffness lasting for 2-3 hours. Notably, she also experienced proximal lower limb weakness, hindering her ability to stand up from a sitting position. The subsequent onset of quotidian fever, ranging up to 103 degrees Fahrenheit, and documented over the past two years, was punctuated by persistent patterns of high fever over the recent four months. This fever was not ameliorated by antipyretics, contributing to unintentional weight loss and decreased appetite.

Two months before her current admission, the patient sought care at a District Headquarters (DHQ) hospital, where she underwent misguided treatment. Following a diagnostic uncertainty, she was initiated on anti-tuberculous therapy (ATT) and corticosteroids, despite a negative QuantiFERON test for tuberculosis. This therapeutic decision was further complicated by the emergence of ATT-induced hepatotoxicity [Table 5] ultimately leading to the cessation of the treatment regimen. Despite the nuanced clinical presentation, previous interactions with healthcare providers yielded temporary relief, often attributed to symptomatic management through medications such as diclofenac and paracetamol.

The patient's recent symptoms continued to evolve, with the emergence of oral ulcers, hair loss, and a sore throat. Periorbital puffiness of the face marked the initiation of generalized body swelling, gradually encompassing the lower limbs, leading to ankle and pedal edema. Simultaneously, she experienced episodes of loose motion and abdominal pain. A subsequent salmon-pink rash accompanied by pruritus emerged, further confounding her clinical presentation.

4.1. Physical Examination Findings on Admission:

The physical examination of the patient upon admission revealed notable clinical findings; Firstly, she exhibited generalized body edema, with a more pronounced presence on her face and upper and lower limbs. The edema exhibited a non-pitting nature. Furthermore, the patient displayed a pale and icteric appearance, hinting at possible hematological or hepatic involvement. The Patient was persistently in sinus tachycardia. Cervical lymphadenopathy was also evident. The patient's fever, characterized by a high temperature of 103 degrees Fahrenheit, was indicative of an active systemic inflammatory process. Additionally, an urticarial maculopapular rash was discerned on the trunk and lower limbs, suggestive of hypersensitivity or immune-mediated reactions. Despite these concerning findings, the examination yielded otherwise normal results for the cardiovascular, central nervous system, gastrointestinal, and respiratory systems, providing reassurance regarding the absence of major organ involvement. However, mild tachycardia was observed, likely attributed to the underlying systemic inflammation and fever. These findings collectively presented a complex clinical picture, reaffirming the need for thorough evaluation and diagnostic precision in the patient's management.

4.2. Diagnostic Pathway

A meticulous approach to her healthcare was undertaken, involving a series of serial baseline laboratory investigations aimed at monitoring her overall health. These investigations included blood complete picture (BCP)[Table 1], liver function tests [table 5], renal function tests [Table 3], and serum electrolytes [Table 4], which collectively provided crucial insights into her physiological well-being and helped track any dynamic changes.

Blood Complete Picture

Reference range ➡	TLC (106/l)	RCC ml/	Hb (g/dl)	HCT (%)	Platelet count/µL
DOA ⬇	4000-10000	3.8-4.8	15 Dec	36-46	200000-550000
1st	4690	3.26	8.4	25.3	70000
2nd	4490	3.58	9.1	28.1	74000
4th	7530	3.66	9.3	28.1	69000
5th	7490	3.22	8.1	25.2	92000
7th	7030	3.46	8.8	26.5	63000
8th	8120	3.65	9.3	29	66000
9th	7300	3.97	9.5	30.8	80000
10th	3610	4.03	10	31.5	85000
12th	5930	2.97	7.4	23.1	98000
13th	3260	3.35	8.4	26.4	146000
14th	4040	3.6	8.6	28	172000
15th	4320	3.47	8.7	27	305000
18th	7930	3.58	9.1	28.1	421000
20th	11580	3.71	9.3	29.1	352000
22nd	11360	3.53	8.9	27.6	277000

DIFFERENTIAL TLC COUNT

Date	TLC (109/l)	Neutrophils (%)	Lymphocytes (%)
	Ref range: 4000-10000	Ref range: 45-70	Ref range: 20-40
1st	4690	40.8	56.9
2nd	4490	53.8	44.5
4th	7530	67	30
5th	7490	61.4	32.8
7th	7030	17.5	81.1
8th	8120	18.7	80.3
9th	7300	21	77
10th	3610	21.2	74.8
12th	5930	44.6	51.9
13th	3260	54.9	40.6
14th	4040	54.3	37.9
15th	4320	50	48.1
18th	7930	36.8	53.7
20th	11580	59.7	36.5
22nd	11360	68.3	29.8

RENAL FUNCTION TESTS

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Date	TLC (109/l)	Neutrophils (%)	Lymphocytes (%)
	Ref range: 4000-10000	Ref range: 45-70	Ref range: 20-40
1st	4690	40.8	56.9
2nd	4490	53.8	44.5
4th	7530	67	30
5th	7490	61.4	32.8
7th	7030	17.5	81.1
8th	8120	18.7	80.3
9th	7300	21	77
10th	3610	21.2	74.8
12th	5930	44.6	51.9
13th	3260	54.9	40.6
14th	4040	54.3	37.9
15th	4320	50	48.1
18th	7930	36.8	53.7
20th	11580	59.7	36.5
22nd	11360	68.3	29.8

SERUM ELECTROLYTES

Day of admission	Na+ (mmol/l)	k+ (mmol/l)	Ca++ (mg/dl)	Cl- (mmol/l)
	Ref range: 138-149	Ref Range: 3.4-4.7	Ref range: 8.5-10.5	Ref range: 98-106
1st	128.2	42.85	-	107.1
4th	127.9	3.36	7.17	-
5th	130.6	4.07	-	-
8th	-	-	7.88	102.8
9th	135.2	4.46	8.05	104.2
10th	-	5.21	-	-
11th	132.9	5.21	-	-
13th	134.6	4.73	-	-
14th	135.1	4.39	-	-
16th	136.5	4.96	-	-
17th	134.9	3.72	8.87	103.6
18th	-	-	8.95	105.2
22nd	137.8	4.13	-	-

LIVER FUNCTION TESTS

Date of admission	Total bilirubin (mg/dl)	ALT (U/l)	ALP (U/l)	Serum Albumin (g/dl)
	Ref range: 0.3-1.2	Ref range: 4-42	Ref range: 35-105	Ref range: 3.3-4.5
1st	7.83	242	242	1.9
4th	5.19	198	440	1.9
5th	4.58	163	441	-
8th	5.1	132	941	-
9th	4.52	118	837	-
10th	4.32	125	814	2.26
12th	2.89	93.1	546	2.53
13th	2.9	224	493	-
14th	2.85	363	486	-
17th	2.8	334	441	3.1
18th	2.44	316	372	3.5
22nd	1.55	135	247	3.8

C-REACTIVE PROTEIN – QUANTITATIVE

Date of admission	CRP-Q (mg/l) Ref range: 0-5
1st	50.7
9th	46.1
18th	11.7

INFLAMMATORY MARKERS

Date of admission	Marker	Result	Reference range
Pre-admission – 1 month	Serum ferritin	12600.4	10-120 ng/ml
2nd	Serum ferritin	160861	10-120 ng/ml
5th	Procalcitonin	6.75	0.5 - 2 moderate risk of sepsis
			2-10 high risk of sepsis
			>10 severe sepsis or SIRS
7th	C-reactive protein-Q	50.4	Negative 0-5
			Positive >5
10th	Heptoglobin	0.12	0.3-2
15th	Procalcitonin	0.25	0.5 - 2 moderate risk of sepsis
			2-10 high risk of sepsis
			>10 severe sepsis or SIRS
16TH	Ferritin	2000	10-120 ng/ml

Initial suspicions pointed towards SLE; however, this diagnosis was ruled out with a Negative RA factor [table 9] and comprehensive ENA profile [Table 8]. Subsequently, two working diagnoses were established: sJIA with MAS and B-cell lymphocytic leukemia.

In parallel, additional specialized laboratory investigations were conducted. These included an extractable nuclear antigens (ENA) profile [Table 8], assessment of inflammatory markers [Table 6

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and 7] , and blood cultures. These specific investigations ruled out specific system failures, systemic lupus erythematosus (SLE), infectious etiologies, and malignancies. Outcomes of these investigations contributed in directing the medical team towards the likely diagnosis.

IMMUNOLOGY ENA PROFILE – 12TH DATE OF

Anti-bodies related to:	Anti-bodies	Result:	Reference Range:
SLE	Anti-Sm	0.1 (negative)	Negative < 5
	Anti DsDNA	0.2 (negative)	Borderline 5-10
			Positive > 10
Sharp syndrome	Anti-RNP	0.2 (negative)	Negative < 5
			Borderline 5-10
			Positive > 10
Sjögren Syndrome	Anti-SSA/RO	0.1 (negative)	Negative < 5
	Anti-SSB/LA	0.2 (negative)	Borderline 5-10
			Positive > 10
Systemic Sclerosis	Anti-Scl-70	0.1 (negative)	Negative < 5
			Borderline 5-10

RA FACTOR TEST

DATE	Result	Reference range
2 MONTHS PRE-ADMISSION	Negative	>14
17TH DAY OF ADMISSION	37.3 (positive)	>14

BONE MARROW ASPIRATE FOR CULTURE AND SENSITIVITY

SPECIMEN	Bone Marrow
REPORT	The culture has not yielded growth of any microorganism after 7 days of incubation at 37°C

BONE MARROW TREPHINE BIOPSY

Parameter	Result
Date of Biopsy	21-07-2023 (9th DOA)
Sample Cellularity	Adequate
Cellularity	Moderately cellular (overall cellularity 45-50%)
Architecture	Preserved
Megakaryocytes	Increased
Erythropoiesis	Relatively depressed
Myelopoiesis	Active showing maturation
Granuloma	1x focal collection of epitheloid cells seen in the inflammatory background of lymphocytes, histocytes forming ill defined granuloma
Reticulin	MF-1
Other features	Histocytes
Opinion:	a) Chronic Granulomatous Inflammation
	b) SecondaryHemophagocytic Lymphohistiocytosis (HLH), as patient is fulfilling following diagnostic criteria: (0) Fever (il) Cytopenias (il) Ferritin (12600ng/ml) (iv) Triglycerides 666 mg/dI (v) Histiocytes & Haemophagocytosis

Radiological investigations

Report 1: Ultrasound Soft tissue Neck (2nd DOA)

Multiple sub centimetric cervical lymph nodes are noted in bilateral cervical chains. One of the lymph nodes measures 4.5mm on its short axis on the right, another measures 4.7mm in its short axis on the left side

Overlying skin and subcutaneous tissue show mild thickening with indistinct haziness and edematous changes in the neck region however no definite collection is noted at the time of the ultrasound.

Report 2: Ultrasound Abdomen & Pelvis (4th DOA):

Liver appears normal in size measuring 15.7cm and shows normal hepatic parenchymal echotexture. No intrahepatic or extrahepatic cholestasis seen. No focal lesion is noted. Gall bladder is contracted. Portal vein and CBD appear normal in caliber. Spleen (10.9cm) appears normal. Mid abdomen is obscured due to excessive bowel gas shadows. Both kidneys are normal in size, shape and contour. No nephrolithiasis seen on either side. Bilateral renal parenchymal echogenicity and thickness appear normal. No renal or adrenal mass seen. Urinary bladder is minimally filled showing free floating internal echoes in it. Mild free fluid is noted in pelvic cavity and cul de sac.

Conclusion: Free floating internal echoes in urinary bladder concerning for cystitis. urine RE correlation is advised. Mild free fluid in pelvic cavity and cul de sac.

Report 3: Ultrasound Abdomen and pelvis (16th DOA)

Liver appears normal in echotexture and size, measuring 15 cm. No intrahepatic or external cholestasis seen. No focal lesion noted. Gall bladder is contracted hence cannot be commented upon. Portal vein and CBD appear normal in caliber. CBD measures 1.3 mm in caliber. Mid abdomen is obscured due to excessive bowel gas shadows. Spleen appears normal. Both kidneys are normal in size, shape and contour. No hydronephrosis or nephrolithiasis

seen on either side. Bilateral renal parenchymal echogenicity and thickness appear normal. No renal or adrenal mass seen. Urinary bladder is empty. No free fluid is noted in peritoneal cavity.
Conclusion Essentially normal ultrasound abdomen.

Report 4: 2-D echocardiogram:
Report: patient in sinus rhythm. LV normal in size and function. No regional wall motion abnormality detected. No pericardial effusion noted.

Radiological investigations were done including; an ultrasound abdomen [Report 2] which revealed hepatomegaly, likely attributed to the anti-tuberculous therapy (ATT) previously received. Serial ultrasound examinations of the abdomen and pelvis [Report 3] indicated a progressive resolution of hepatomegaly while providing evidence of cystitis, further contributing to the pool of signs and symptoms. The ultrasound (USG) examination of the neck [Report 1] reveals the presence of multiple sub-centimetric cervical lymph nodes observed in bilateral cervical chains. Among these, one lymph node measured 4.5mm on its short axis on the right side, while another measured 4.7mm in its short axis on the left side. Additionally, the examination also noted mild thickening of the overlying skin and subcutaneous tissue, along with indistinct haziness and edematous changes in the neck region. It's important to highlight that no definite collection or abnormal accumulation is detected at the time of this ultrasound assessment.
Finally, bone marrow histopathology [Table 11] and cultures [Table 10], were pursued diligently to explore potential malignancies and latent tuberculosis. Despite thorough examination, these investigations yielded no evidence of malignancies or latent tuberculosis. sJIA is a diagnosis of exclusion. The Bone marrow studies [Table 11] confirmed suspicion of HLH (secondary MAS). It was at this juncture that an Interferon-Gamma Release Assay (IGRA) test conclusively ruled out latent tuberculosis led to the diagnosis sJIA with MAS, highlighting the meticulous and thorough nature of this diagnostic journey.

5. Treatment
A treatment plan was devised in order to address both long-term management of sJIA and short-term life-threatening complications of the patient's condition. The Rheumatology department was consulted and the patient was shifted to their department for further comprehensive treatment.

1. **Anti-inflammatory and Immunosuppressive Therapy:**

- NSAIDs: To manage arthritis symptoms and control inflammation.
- Glucocorticoids: High-dose corticosteroids (e.g., prednisolone) to rapidly control systemic inflammation and MAS. Taper gradually based on clinical response.
- Biologic Agents:
- Anakinra: An IL-1 receptor antagonist to control systemic inflammation.
- Tocilizumab: An IL-6 receptor antagonist if there's an inadequate response to Anakinra.
- Canakinumab: An alternative IL-1 inhibitor, especially useful in controlling recurrent MAS.
- Methotrexate: As a disease-modifying antirheumatic drug (DMARD) for long-term management of sJIA.

2. Management of Macrophage Activation Syndrome (MAS):

- High-dose corticosteroids: As first-line treatment.
- Cyclosporine: To suppress immune system hyperactivity, especially in severe MAS cases.
- Intravenous immunoglobulin (IVIG): For immune modulation and support during acute MAS flares.

3. Supportive Care:

- Hydration and Nutrition: Ensure adequate hydration and nutritional support to address weight loss and decreased appetite.
- Physical Therapy: To maintain joint function and muscle strength, especially considering proximal lower limb weakness.

5. Discussion
Macrophage activation syndrome (MAS) is a critical and life-threatening complication of systemic juvenile idiopathic arthritis (sJIA), presenting as an overwhelming inflammatory response that is clinically and histopathologically similar to hemophagocytic lymphohistiocytosis (HLH). The clinical overlap with HLH complicates the diagnostic picture, as the stringent criteria developed for HLH may not be entirely appropriate for the early detection of MAS in the context of sJIA, potentially delaying crucial treatment interventions [12,13]. Genetic studies have provided insight into this overlap, revealing protein-altering variants in HLH-associated genes in some patients with sJIA and MAS, pointing to a shared pathophysiological basis [14].
The emergence of biologic therapies targeting interleukins, such as IL-1 and IL-6 inhibitors, has transformed the treatment landscape of sJIA, potentially altering the clinical presentation of MAS and, as a consequence, the interpretation of diagnostic tests. These therapies may attenuate the classical clinical features of MAS, challenging clinicians to recognize and diagnose early MAS accurately [15]. This shift necessitates a reevaluation of the diagnostic criteria and a development of new tools, sensitive and specific to MAS in the setting of sJIA, treated with modern biologics.
The complexity of diagnosing MAS in sJIA is further highlighted by the potentially misleading "normal" levels of blood tests in patients with systemic JIA who are in the early stages of MAS. The interpretation of these tests requires a nuanced understanding that "normal" levels may, in fact, indicate a decline from previously elevated levels due to sJIA, thus signifying the onset of MAS [16]. To address this, various diagnostic criteria and scoring tools have been proposed, aiming to provide a more nuanced and clinically useful diagnostic approach for MAS in sJIA patients [12,16,17].
In the setting of the current case, the patient presented a diagnostic conundrum that encapsulated the challenges discussed above. The clinical trajectory, marked by prolonged fever, arthritis, and the emergence of symptoms indicative of MAS, required a holistic diagnostic approach. The adaptation of the HLH-2004 guidelines to the sJIA context, the preliminary 2004 MAS guidelines, and the 2016 classification criteria for MAS in sJIA have all contributed to the formulation of a robust diagnosis [16,17]. The development and validation of diagnostic scoring tools such as the MAS/sJIA

(MS) score and the MAS-HLH (MH) score, utilizing multinational patient data, have also been instrumental in refining the diagnosis of MAS in the setting of sJIA, distinguishing it from primary HLH with high sensitivity and specificity [18,19].

6. Conclusion

The case elaborates the vital importance of recognizing and treating MAS as an emergency in patients with sJIA. Given the potential for biologic therapies to modify the clinical expression of MAS, clinicians must be vigilant and adapt their diagnostic strategies accordingly. High-dose glucocorticoids remain the cornerstone of emergent treatment for MAS, with additional therapies such as cyclosporine, cyclophosphamide, etoposide, or anakinra being implemented in refractory cases [20,21]. The case highlights the evolving nature of sJIA and MAS, the impact of biologic therapies on disease presentation, and the need for ongoing research into effective diagnostic and therapeutic strategies. It also emphasizes the importance of a multidisciplinary approach in managing such complex cases, with a focus on early recognition and treatment to improve outcomes for patients with this severe complication of sJIA.

7. Abbreviations: sJIA - Systemic Juvenile Idiopathic Arthritis; MAS - Macrophage Activation Syndrome; HLH - Hemophagocytic Lymphohistiocytosis; ATT - Anti-Tuberculous Therapy; IL - Interleukin (e.g., IL-1, IL-6); CRP - C-Reactive Protein; ESR - Erythrocyte Sedimentation Rate; ANA - Antinuclear Antibodies; ENA - Extractable Nuclear Antigen; MRI - Magnetic Resonance Imaging; IVIG - Intravenous Immunoglobulin; CBC - Complete Blood Count; ALT - Alanine Aminotransferase; AST - Aspartate Aminotransferase; LFTs - Liver Function Tests; RFTs - Renal Function Tests; NSAIDs - Nonsteroidal Anti-Inflammatory Drugs; DMARDs - Disease-Modifying Antirheumatic Drugs; TNF - Tumor Necrosis Factor; JIA - Juvenile Idiopathic Arthritis; AOSD - Adult-Onset Still's Disease; SLE - Systemic Lupus Erythematosus; CT - Computed Tomography; USG - Ultrasound; PPD - Purified Protein Derivative (Tuberculosis Test); IGRA - Interferon-Gamma Release Assay

8. Declarations

Ethics approval and consent to participate

This case report adheres to ethical principles governing medical research and patient confidentiality. Informed consent was obtained from the patient for the publication of this case report, including the use of clinical data, images, and relevant medical history. All patient identifiers have been removed or anonymized to protect confidentiality. The report was conducted with integrity, honesty, and respect for the patient's autonomy, dignity, and privacy. It aligns with the principles outlined in the Declaration of Helsinki and other relevant ethical guidelines. The authors declare no conflicts of interest or financial disclosures related to this case report.

Consent for publication

Written informed consent was taken from the patient's legal guardians based on the journal's policy. Consent for publication is also provided by the patient's legal guardians abiding to the policy of the journal.

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