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Mucormycosis after liver transplant: Case series and literature review

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ABSTRACT

We describe two cases of possible healthcare-associated mucormycosis in liver transplant recipients. Mucorales may be acquired from environmental sources such as contaminated medical equipment, grafts or procedure related. Gastrointestinal mucormycosis is the second most common presentation in healthcare-associated infections.

The high mortality rate of mucormycosis is due to low suspicion, insensitive diagnostic tests and rapid angioinvasion. Early antifungal treatment and surgical debridement are imperative to improve survival.

1. Introduction

Mucormycosis is caused by fungi from the order Mucorales, with *Rhizopus* spp., *Mucor* spp., and *Lichtheimia* spp. (formerly *Absidia*) accounting for over 90 % of all cases [1] Its incidence has been increasing recently due to the growing number of immunocompromised patients associated with corticosteroids, prolonged neutropenia and antifungal prophylaxis that lack activity against Mucorales [2,9,10]

Mucormycosis is an infrequent complication of solid organ transplantation (SOT), with estimated incidence ranging from 0.4 % to 16 % and an overall incidence of 0%–2% in liver recipients [3,4]. However, it has a high fatality rate, with a 90-day survival of 50–60 % [5].

Among all forms of invasive mucormycosis, primary gastrointestinal disease is one of the rarest manifestations. Any portion of the gastrointestinal tract can be affected, but gastric and colonic involvement are the most frequently. Ulcers are the most common manifestation, often large, with rolled, irregular edges that may mimic malignancy, as well as angioinvasive lesions leading to thrombosis, infarction, and necrosis [6,7].

Mortality in gastrointestinal infection is high, approaching 40–50 %. However, patients may have increased survival when antifungal treatment is combined with surgical resection [6,8].

2. Case

From 2018 to 2023, 234 liver transplants were performed in our center, of which two (0.8 %) developed mucormycosis.

2.1. Case 1

A 39-year-old woman presented with acute liver failure secondary to hepatitis A in May 2023. She exhibited progressive neurological deterioration, required mechanical ventilation, and was admitted to the ICU. Imaging studies showed cerebral edema. After two days, she underwent orthotopic liver transplant using the Piggyback Face to Side technique. She only received methylprednisolone as the induction regimen after liver transplant due to a local basiliximab shortage. Postoperative doppler ultrasound showed no focal lesions and permeable vascular structures in the liver graft. The donor was a previously healthy 19-year-old female who suffered a traumatic brain injury after a 3.5m fall.

Following surgery, the patient's neurological status did not improve. A brain CT scan revealed a parietal intracranial hemorrhage of 35.6 ml, which was managed conservatively. Immunosuppression therapy was initiated with mofetil mycophenolate and tacrolimus. Two days later, successful extubation was achieved, and after four days post-transplant,

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enteral nutrition was initiated. Blood tests showed progressive elevation of liver enzymes, prompting a Doppler ultrasound that indicated a possible hepatic artery stenosis, requiring anastomotic balloon dilatation.

Eleven days after transplant, she experienced multiple episodes of hematochezia. Colonoscopy revealed a 3 cm Forrest III ulcer in the cecum and a 3 × 1 cm Forrest IIb ulcer in the transverse colon at the hepatic angle, covering 50 % of the circumference. Due to suspected cytomegalovirus infection, biopsies were taken, along with a serum viral load test, resulting in 35 UI/mL. Empirical treatment with ganciclovir and ertapenem was started.

Histopathologic exam revealed a colon ulcer biopsy with extensive areas of necrosis, and evidence of thick non-septated hyphae (Fig. 1) Due to high suspicion of colonic mucormycosis and intestinal microperforation, liposomal amphotericin B (5 mg/kg or 300 mg/day) and meropenem were started, mofetil mycophenolate therapy was stopped. An emergency exploratory laparotomy was performed, leading to a total colectomy with a terminal ileostomy (Fig. 2).

Intrabdominal abscess culture reported the growth of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Bacteroides thetaiotaomicron* for which she received an 8 day course of carbapenems. A follow-up CMV viral load test reported 387 UI/mL. Additionally, *Lichtheimia ramosa* (Fig. 3) was reported by MALDI-TOF MS (Bruker) from colonic biopsy ten days later, liposomal amphotericin B was continued.

A contrast-enhanced abdominal CT scan showed ascites with peritoneal enhancement, inflammatory changes in the jejunum and rectum, incipient intraabdominal collection in the subcutaneous fat underlying the staple lines in the anterior and right lateral abdominal wall. Also, bilateral pleural effusion, more pronounced on the right hemidiaphragm, without lung infiltrates, and a generalized increase in the size of the liver graft, spleen, and kidneys were also noted.

Pleural fluid analysis revealed an exudative effusion without isolation of any bacteria or fungi. Rectosigmoidoscopy showed no further microbiological or histopathological evidence of fungal invasion in sigmoid biopsies. Twenty-eight days after hemicolectomy (considered as the primary source control of infection), liposomal amphotericin B treatment was suspended and mofetil mycophenolate reinitiated.

After a 47-day hospital stay, the patient was discharged for further evaluation in an outpatient setting. There was no recurrence of the disease at the one-year follow-up.

2.2. Case 2

A 64-year-old male with biliary cirrhosis secondary to benign biliary tract injury underwent orthotopic liver transplant in June 2018. Cava replacement technique was used. Other relevant past medical history included vitiligo, hypothyroidism and acute cholangitis one month prior. The donor was a 17-year-old male who suffered a traumatic brain injury due to a motorcycle accident, leading to a 3-day-stay in the ICU until organ procurement.

During surgery, the patient experienced bleeding of 2000 ml secondary to coagulopathy, requiring vasopressor therapy. Methylprednisolone and basiliximab were used for induction. Following persistent hemodynamic instability and a decline in hemoglobin levels, a reintervention was performed, revealing hemoperitoneum (1000 ml) with layered bleeding requiring abdominal packing. Vasopressor therapy was discontinued on the 5th day post-surgery. He was extubated and maintenance immunosuppression with 20 mg prednisone and tacrolimus-based therapy initiated on the 6th day.

On the 9th day post-transplant, he developed a fever and persistent abdominal pain with ileus, prompting conservative management with nasogastric tube insertion. Due to partial improvement, CT was performed, revealing areas of hypoperfusion in the liver graft accompanied by gas (Fig. 4). Antimicrobial therapy with meropenem and vancomycin was initiated. Doppler ultrasound of the graft demonstrated decreased echogenicity and vascularity in the hepatic dome.

At 12 days post-transplant, a liver biopsy was conducted. Two days later, the histopathological report showed non-septated hyphae with angioinvasion, consistent with mucormycosis, prompting the initiation of liposomal amphotericin B (7 mg/kg or 400 mg/day) (Fig. 5). The liver biopsy culture showed Rhizopus spp by Bruker Biotyper Matrix-Assisted Laser Desorption Ionization (MALDI-TOF) (Fig. 6).

Four days later, partial hepatectomy was performed, revealing discoloration in segments 5, 6, 7, and 8, as well as at the diaphragmatic level. The patient was admitted to the ICU due to refractory septic shock. Unfortunately, he died hours later.

3. Discussion

We describe two cases of mucormycosis occurring early after liver transplant: one case with colonic involvement and another likely donor-derived, occurring eleven and seven days after transplant, respectively. In the first case, a successful outcome was achieved after four weeks of antifungal treatment and complete resection through total colectomy. In contrast, the second case involved extensive graft involvement and hemodynamic instability, which delayed surgical intervention and impeded complete resection. These cases uniquely illustrate the potential morbidity of fungal invasion in immunosuppressed patients after

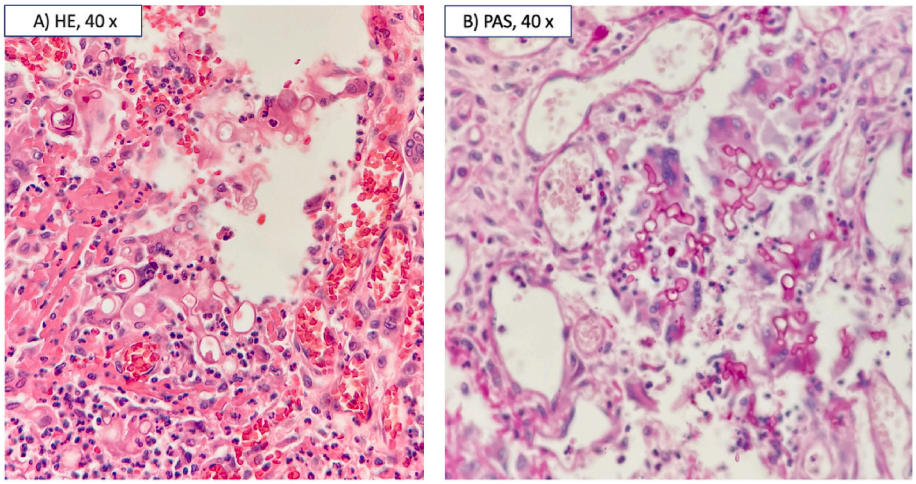

Fig. 1. A) Hematoxilin & Eosin stain showed non-septate broad, ribbon-like hyphae with neutrophilic infiltrate. **B) Periodic acid-Schiff (PAS)** stain highlighting the presence of broad-based, irregularly branching hyphae.

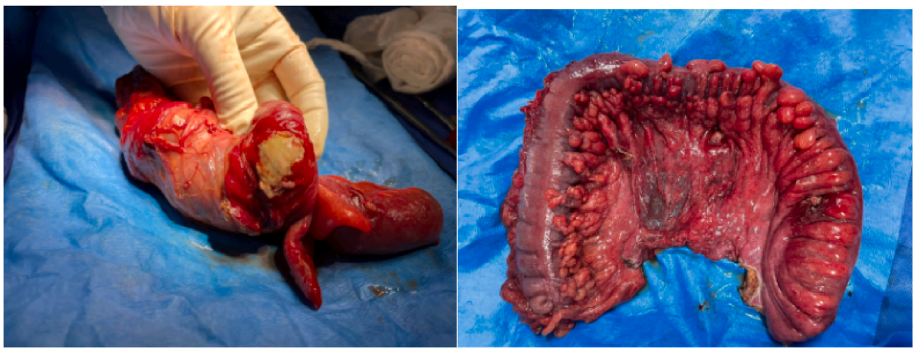

Fig. 2. A. Macroscopic view of the cecal ulcer. **B.** A total colectomy was performed with complete mesocolic excision. Three ulcers were found in the colon mesenterium.

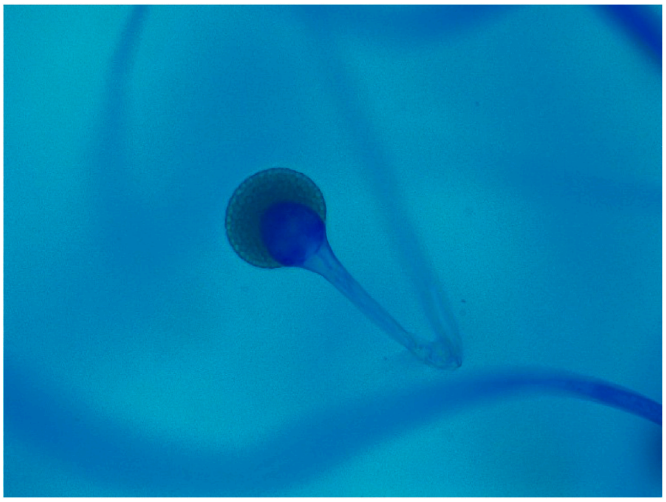

Fig. 3. Colonic ulcer biopsy observation 40x, lactophenol blue stain: Spherical sporangiophore with abundant sporangiospores.

liver transplant.

In a review of healthcare-associated mucormycosis, cutaneous infection was the most common presentation (57 %), followed by gastrointestinal tract involvement (15 %). The major underlying diseases associated with healthcare-associated mucormycosis include solid organ transplantation (SOT) (24 %) and diabetes mellitus (22 %) [4].

Predisposing factors for the development of mucormycosis after liver transplant include the use of corticosteroids, neutropenia, renal failure, prior antifungal prophylaxis with voriconazole or caspofungin (26 %), as well as cholestasis, multiple transfusions, bacterial coinfection, and re-transplantation [9,10]. In case 1, only conventional immunosuppression was present, whereas in case 2, the patient received multiple hemoderivative transfusions in addition to conventional immunosuppression.

Although mold infections typically present late in SOT, early infections after liver transplant, including those caused by Mucorales, can occur, with a reported time to infection of 2.7 months [11]. The very early presentation of these cases within the first two weeks raised suspicion of healthcare-associated mucormycosis.

The highest incidence of mucormycosis is observed among recipients of lung transplants, while the lowest is seen in those who have undergone renal transplants [12] In a retrospective review, 52 % of the 27 patients with gastrointestinal mucormycosis were SOT recipients [7].

Immunosuppressed patients may contract Mucorales infections from environmental sources (e.g., construction sites, negative pressure rooms, water leaks), graft associated transmission or contaminated medical equipment. Several outbreaks have been described, related to contaminated medical equipment such as non-sterile adhesive dressings, bandages, hospital linen, insulin pumps, ostomy bags, feeding solutions, or during invasive procedures and surgery [4,9,13]. The initial

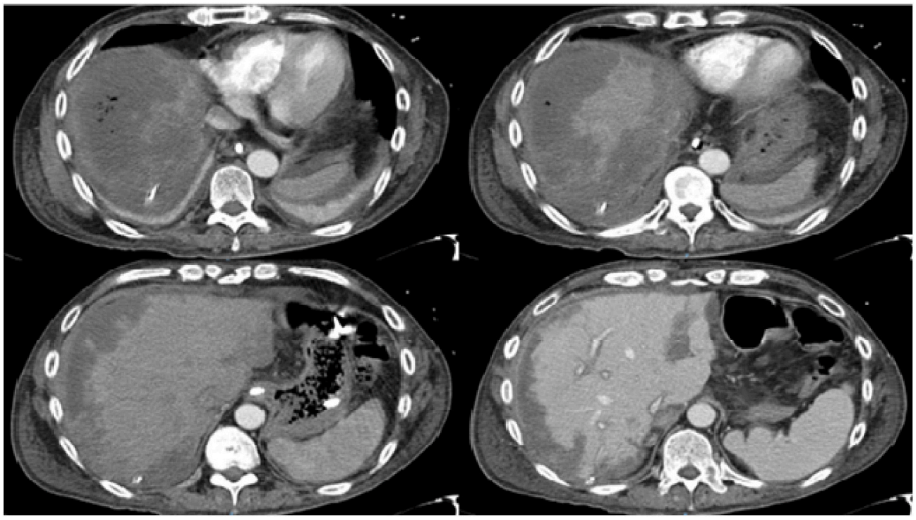

Fig. 4. Abdominal contrast CT scan: Liver with heterogeneous density related to multiple hypodense, peripheral, diffuse areas, without enhancement, the most extensive in the hepatic dome, occupying segments VII and VIII, with added gas bubbles. Perihepatic fluid, (medial to segment VI), suggestive of residual blood.

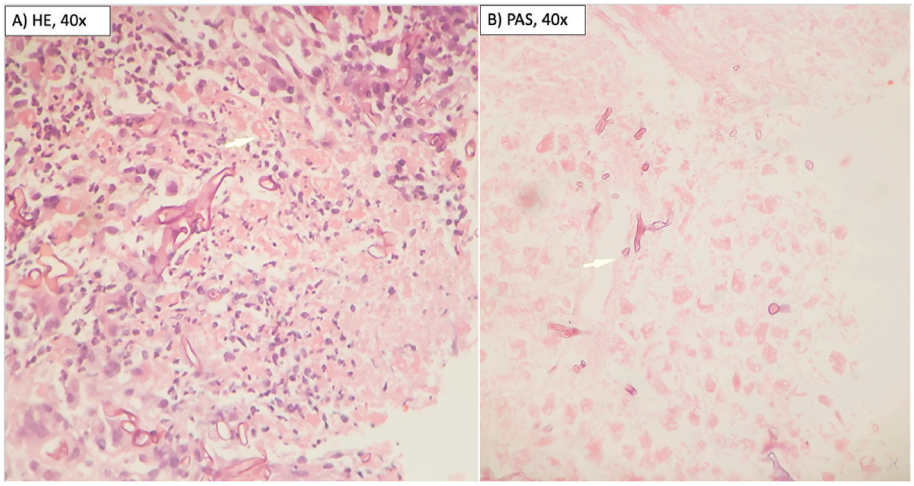

Fig. 5. A. **A) Hematoxilin & Eosin stain (HE)** showing destruction of parenchyma, acute and chronic inflammation with presence of thick non-septate hyphae. **B) Periodic acid-Schiff (PAS)** stain with broad-based, irregularly branching hyphae.

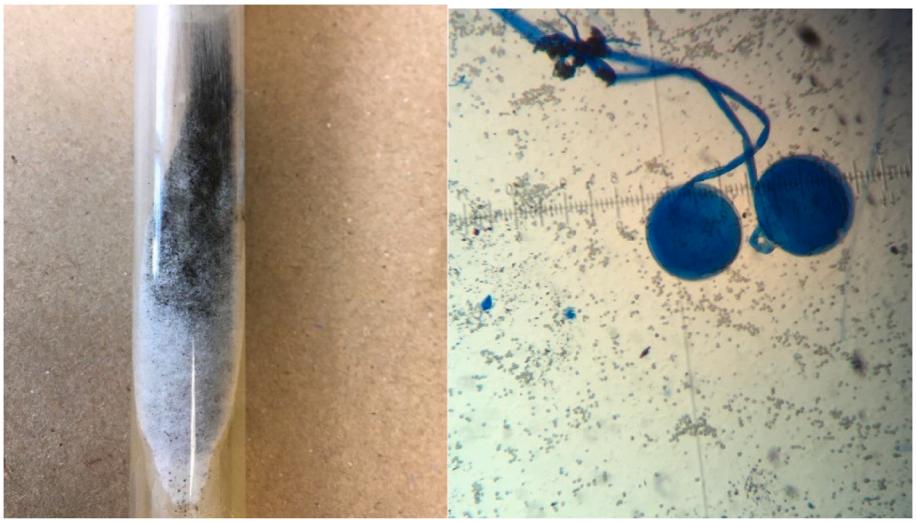

Fig. 6. A. Sabouraud Agar at 5 days at 30 °C. Aerial mycelial growth covering the agar surface with fluffy colonies resembling cotton candy, initially white in color, turning gray or brownish-gray. The colony's reverse side shows a whitish color without pigment. **B. Lactophenol blue stain 10X of liver biopsy**: Thick hyphae, sporangiophores approximately 100 μm in diameter, columella at the base of the sporangiophore, and abundant scattered spores.

presentation of the infection can provide information about the specific site where spores were introduced [13].

Potential causes of healthcare-associated gastrointestinal mucormycosis include the use of wooden tongue depressors (as wood serves as a natural substrate for mucormycetes) in the preparation of oral medications, contamination of supplements, pre-packaged food/enteral solutions, insertion of contaminated naso/orogastric tubes, or the use of contaminated peritoneal catheters [13]. Gastrointestinal mucormycosis poses the greatest challenge for diagnosis due to its nonspecific manifestations and low suspicion. The incidence rate accounts for 5–13 % of all mucormycosis cases, with the majority being diagnosed incidentally during surgery or postmortem examinations [14].

The most common sites of mucormycosis with gastrointestinal involvement include the large intestine (43 %), stomach (33 %), small intestine (28.4 %), and esophagus (3.4 %). Nonetheless, in solid organ transplantation (SOT), gastric involvement is the prevailing presentation, followed by intestinal disease [7,9].

Regarding clinical manifestations, the most frequent presentations include abdominal pain (35.3–68 %), gastrointestinal bleeding (34–48 %), abdominal distension (49.7 %), and diarrhea (8 %) [9] In 200 cases of gastrointestinal mucormycosis, the mortality rate was 60.5 %, significantly higher in patients who required ventilation and presented with hematochezia, diarrhea, constipation, sepsis, and involvement of both small and large intestines [14].

Our patients presented as isolated cases at different time frames. An increase in the basal frequency of mucormycosis was not identified during those times. No other cases of surgical, procedure-associated, or gastrointestinal mucormycosis occurred. In the first case, we cannot rule out the possibility of ingestion through the nasogastric tube and/or contaminated enteral nutrition, given that the gastrointestinal tract was the only affected organ. No environmental or medical equipment sampling was performed. In the second case, donor-derived mucormycosis was suspected as the primary cause. Although the macroscopic view of the liver was normal at the time of transplant, the donor had suffered a traumatic accident with possible skin involvement and potential hematogenous dissemination to non-contiguous organs. Although Mucorales can disseminate and grow in blood cultures, no other organs were involved in the recipient. Contamination of the transport equipment cannot be ruled out, and we were not able to retrieve any information from the rest of the possible recipients. Another possible hypothesis is

contamination of surgical instruments and/or materials during the multiple surgical interventions the patient underwent due to coagulopathy, but no additional surgery-related mucormycosis occurred within the time frame.

Diagnosis typically requires an invasive procedure to sample sterile sites and is based on culture or histopathological analysis. Direct microscopy with fluorescent stains is recommended since cultures may lack sensitivity. Fungal stains (e.g., Grocott, Calcofluor white) reveal broad, ribbon-like, nonseptate hyphae with irregular walls and 90° angle branching. Microscopic morphological characteristics can aid in identifying the genus, but highly trained personnel are needed. Molecular diagnosis through validated PCRs or sequencing of the ITS region is encouraged, particularly in outbreak investigations for improved epidemiological characterization. Novel techniques such as MALDI-TOF are promising but rely on commercial libraries that may lack sufficient diversity for accurate species identification [1,5,15].

The mortality rate of mucormycosis is usually elevated (>50 %) but is particularly higher when surgical debridement is not performed (85.7 % vs. 37.3 %). Gastrointestinal mucormycosis can reach an 85 % mortality rate, primarily due to bowel perforation, but this rate is reduced when surgical resection is feasible (20.4 % vs. 62.1 %) [4,8,14,16].

The use of Liposomal amphotericin B remains as the first line of therapy. Range dose from 5 to 10 mg/kg per day is recommend. When CNS involvement exists, high dose of 10 mg/kg must be indicated [15]. Isavuconazole has also been licensed as a first-line treatment after a multicenter open-label study demonstrated similar efficacy. "Step--down" therapy may include posaconazole or isavuconazole [15,17].

While no randomized data on the use of posaconazole exist, it can still be an option for patients with refractory disease, those intolerant to L-AMB, or those needing prolonged continuation or maintenance therapy [17].

Limited data support the use of combination antifungal therapy [18]. A small trial of rhino-orbito-cerebral mucormycosis showed improved survival with liposomal amphotericin B (LAmB) plus an echinocandin, but no benefit was observed in patients with hematological malignancies [19]. Salvage therapy for refractory infections may include isavuconazole, posaconazole, or combined therapy [19,20].

The first case received empirical dual antifungal therapy with liposomal amphotericin B (LAmB) and isavuconazole for 4 days, followed by 4 weeks of LAmB. The optimal treatment duration has not been determined, but guidelines recommend prolonged therapy until the resolution of signs and symptoms of infection, with weekly re-assessment [15]. Decisions about when to stop treatment should be individualized. In the first case, the decision was based on surgical resection, a complete clinical response, and follow-up biopsies showing no further evidence of fungal infection.

Reduction of immunosuppression is also a recommended strategy to support antifungal therapy while balancing the risks of transplant organ rejection. Calcineurin inhibitors have been found to act synergistically with antifungal agents to improve efficacy and survival [20]. In the first case, tacrolimus and prednisone-based immunosuppression therapy was maintained during hospitalization to prevent acute rejection. In the second case, immunosuppression therapy was stopped.

These cases underscore the importance of early diagnosis, prompt initiation of antifungal therapy, and surgical debridement within a multidisciplinary approach, all of which impact survival [8].

CRediT authorship contribution statement

Brenda Aceves-Sánchez: Writing – original draft, Investigation, Conceptualization. **Estefano Rojas-Castañeda:** Visualization, Investigation. **Alfredo Ponce-de-León:** Writing – review & editing, Supervision. **Álvaro López- Iñiguez:** Supervision, Resources. **Andrea Rangel-Cordero:** Resources. **Emilio Sánchez:** Resources. **Noel Salgado-Nesme:** Supervision. **María F. González-Lara:** Writing – review & editing, Supervision, Investigation.

Ethical form

Written informed consent was obtained from the patient and legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Consent

Please declare that you have obtained written and signed consent to publish the case report from the patient or legal guardian(s).

Please state that consent has been obtained from the patient or legal guardian(s)

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Conflict of interest

Please declare any financial or personal interests that might be potentially viewed to influence the work presented. Interests could include consultancies, honoraria, patent ownership or other. If there are none state 'there are none'.

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