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# Intestinal atresias and intestinal failure in patients with *TTC7A* mutations

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ABSTRACT

Mutations in the tetratricopeptide repeat domain 7A (*TTC7A*) gene are associated with severe intestinal disorders and combined immunodeficiency (CID), with poor long-term survival. This study describes the characteristics and clinical course of six patients with intestinal failure who were found to have biallelic *TTC7A* mutations, highlighting key management strategies for identifying these patients and improving their survival. Of the six patients included, five had multiple intestinal atresias (83%) and one had congenital enteropathy (17%). Pyloric web or atresia was present in 100% of patients. All patients had low $CD3^+$ T-cell counts on flow cytometry, consistent with CID. Immunologic management consisted of intravenous immunoglobulin and antibiotic prophylaxis, while two patients (33%) underwent stem cell transplantation. All patients were initially dependent on parenteral nutrition, but two (33%) achieved enteral autonomy after undergoing intestinal transplantation. Patients were followed for a median of 7 years (IQR 4.75–9.25), with a long-term survival rate of 67%. The high incidence of pyloric atresia in this case series suggests that the presence of pyloric atresia, especially in the setting of other intestinal disorders, should prompt screening for CID and a genetic evaluation. Recognition of the mutation and involvement of appropriate interdisciplinary care teams are essential for optimizing survival of these complex patients.

## 1. Introduction

Hereditary mutations of the tetratricopeptide repeat domain 7A (*TTC7A*) gene are a rare cause of gastrointestinal disorders resulting in intestinal failure [1]. Case reports have linked *TTC7A* mutations with a range of phenotypes including various combinations of multiple intestinal atresia (MIA), congenital enteropathy, inflammatory bowel disease (IBD), and immunodeficiency [2,3].

*Abbreviations:* TTC7A, Tetratricopeptide 7A; CID, Combined immunodeficiency; IBD, Inflammatory bowel disease; MIA, Mulitple intestinal atresias; SCID, Severe Combined Immunodeficiency; WES, Whole exome sequencing; TREC, T cell receptor excision circles; IVIG, Intravenous immunoglobulin; HLA, human leukocyte antigen.

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The reported mortality of patients with biallelic *TTC7A* mutations is approximately 70%, with a median survival less than 12 months [3,4].

The *TTC7A* locus encodes for a protein with a variety of functions including cell cycle regulation, cellular organization, and epithelial cell polarity. Dysfunction of this protein results in abnormal intestinal and thymus epithelium, leading to a spectrum of gastrointestinal and immunologic conditions. Due to T cell lymphopenia, patients can present with immunodeficiency, either combined immunodeficiency (CID) or severe combined immunodeficiency (SCID), which leads to vulnerability to severe infections. Patients with biallelic highly destabilizing mutations and consequent loss of protein expression are thought to have worse clinical outcomes, while those with more tolerant missense mutations are likely to experience milder symptoms. Currently, definitive diagnosis requires genetic testing, with initial mutations first identified by whole exome sequencing (WES). Timely confirmation of diagnosis and intervention are important and depend on early recognition of characteristic gastrointestinal mucosal changes [5] and immunologic dysfunction.

As of December 2018, all 50 states in the United States are screening for SCID by measuring T cell receptor excision circles (TREC) on routine newborn screening. TRECs are generated during T cell receptor rearrangement in the thymus, and low or absent TRECs are a marker of T cell lymphopenia. In order to prevent delayed treatment of immunologic dysfunction prior to patients with *TTC7A* mutations undergoing significant surgical intervention, immunology work-up for T cell lymphopenia by lymphocyte subset analysis and/or TREC assay should be pursued. Prompt recognition and treatment of immunodeficiency can prevent severe infections, postoperative complications, and death.

This case series is focused on 6 patients who presented with intestinal failure and were subsequently found to have immunologic dysfunction and biallelic mutations at the *TTC7A* locus. The clinical course and diagnostic work-up for each patient are presented. A review of the management and outcomes of this group of patients is included, with the emphasis on early diagnosis of the genetic mutation and prompt treatment of immunodeficiency leading to improved outcomes. This study was approved by the Boston

**Table 1**
Characteristics of patients with severe intestinal failure and combined immunodeficiency with *TTC7A* mutation.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Gestational Age (weeks) | 37 | 35 | 33 | 34 | 37 | 35 |
| Birth Weight (kg) | 2.51 | 1.5 | 1.86 | 2.39 | 1.9 | 2.39 |
| Follow-up Time (years) | 10 | 7 | 7 | 3 | 0.42 | 22 |
| *TTC7A* Mutation | Compound heterozygous (p.K606R, p.S672P) | Compound heterozygous (exact mutation unknown) | Homozygous (c.674delA, p.H225fs) | Compound heterozygous c.211G > A(p.Glu71Lys) c.911delT(p.Leu304Argfs) | Homozygous (c.1039dup, p.Leu347Profs*38) | Compound heterozygous (c.2470dup, p.Gln824Profs*11 and c.1802+3G > C) |
| Intestinal Failure Etiology | Multiple intestinal atresias | Multiple intestinal atresias | Multiple intestinal atresias | Pyloric atresia, Congenital enteropathy | Multiple intestinal atresias, malrotation with volvulus | Multiple intestinal atresias |
| Low TREC | Yes | Yes | Yes | Unknown | Yes | Unknown |
| T cell ($CD3^+$) count at diagnosis | 100 | 564 | 556 | 132 | 63 | 916 |
| Pyloric Atresia | Yes | Yes | Yes | Yes | Yes | Yes |
| Colonic Atresia | Yes | Yes | Yes | No | Yes | No |
| Pre-transplant Citrulline Level (umol/L) | 6 | 2 | 3 | Unknown | 7 | Unknown |
| Pre-transplant Residual Bowel Length (cm) | 20 | 9 | 25 | Full complement | 10 | Unknown |
| Pre-transplant % Expected Bowel Length | 5.4 | 4.7 | 16.9 | N/A | 6.2 | Unknown |
| Neurodevelopmental Delay | Normal | Normal | Increased Tone, Disconjugate Gaze, Motor and Language delay | Normal | Normal | Global delay |
| Dermatologic Manifestations | Hyperkeratosis, fine white hair | NA | Dry skin, hyperkeratosis | Excessively dry skin | NA | NA |
| Nutritional source at last follow up | 100% oral | 100% PN/Fish oil emulsion | 100% PN/Fish oil emulsion | 89% PN/Combination lipid emulsion, 11% enteral | 100% PN/Fish oil emulsion | 100% oral |
| Weight-for-age Z score at last follow up (if age>2 years) | −1.62 | −0.4 | −0.97 | N/A | N/A | −1.85 |
| BMI Z score at last follow up (or weight-for-length Z score if age <2 years) | 0.13 | −0.3 | 0.81 | 0.02 | −1.82 | −0.43 |

Children's Hospital Institutional Review Board under protocols P00030374 and M06-01-0049.

## 2. Case report

### 2.1. Presentation of case 1

Case 1 is a full-term male who presented with meconium peritonitis requiring an emergency laparotomy. He was found to have pyloric, small bowel, and colonic atresias, which required multiple resections with proximal diversion. Universal Newborn Screening showed low TRECs, suspicious for SCID, and diagnosis was confirmed on further immunologic evaluation which revealed CD3 count <100 cells/microliter. WES identified a compound heterozygous mutation in the *TTC7A* gene (Table 1). SCID was managed with intravenous immunoglobulin (IVIG) replacement therapy and antibiotic prophylaxis (Table 2). Nutritionally, he was maintained on full parenteral nutrition (PN). He received an allogeneic bone marrow transplant without chemotherapy conditioning at 3 months of age from his human leukocyte antigen (HLA) partially matched (9/10) brother. The genetic and immunologic aspects of his management have been previously reported [6,7]. After successful reconstitution of T cell numbers and function, he then underwent a pyloroplasty, multiple stricturoplasties, bowel resections, and creation of an end ileostomy at 11 months of age. Post operatively, his course was complicated by recurrent strictures leading to feeding intolerance and chronic pancreatitis (Fig. 1). Despite receiving hepatoprotective PN with fish oil lipid emulsion, he also developed significant liver dysfunction. A multivisceral transplant was performed at age 5, after which he was able to be weaned from PN. At most recent follow up (age 10), he was entirely orally fed with a weight-for-age Z-score (WAZ) of −1.62, and he had no evidence of neurodevelopmental disability (Table 1).

### 2.2. Presentation of case 2

Case 2 is a preterm female born at 35 weeks gestational age (GA) who presented with neonatal bowel obstruction, and pre-operative work-up was suspicious for MIA. She underwent laparotomy with multiple small bowel and colon resections and gastrostomy tube placement. TREC assay was sent and showed absent TRECs concerning for SCID, and immunologic evaluation confirmed T cell lymphopenia. IVIG therapy was started in conjunction with anti-microbial prophylaxis (Table 2). A compound heterozygous mutation in *TTC7A* was identified via WES. She developed recurrent strictures leading to sustained feeding intolerance (Fig. 2). Serial jejunal balloon dilations were unsuccessful in establishing bowel continuity, resulting in long-term PN dependence. Of note, her course was also complicated by recurrent cholangitis. At age 6, she received a cord blood transplant from her younger brother without chemotherapy conditioning for treatment of her immunodeficiency. She remained fully dependent on PN and fish oil-based lipid emulsion, and she was ultimately listed for multivisceral transplant but died from severe electrolyte disturbances and fluid overload while awaiting transplant.

### 2.3. Presentation of case 3

Case 3 is a preterm male born at 33 weeks GA who underwent exploratory laparotomy for feeding intolerance several days after birth. Intraoperative findings included malrotation with MIA and microcolon. A staged operative approach was taken due to intraoperative instability, ultimately resulting in multiple bowel resections and gastrostomy tube placement. His TREC assay demonstrated absent TRECs, suspicious for T cell lymphopenia. Subsequent immunologic work-up confirmed the diagnosis of CID, and antimicrobial

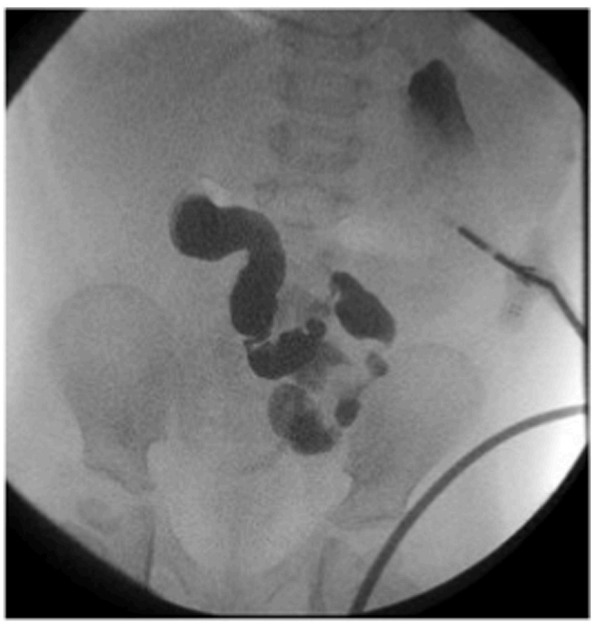

**Fig. 1.** Upper GI series from patient 1 (age 4), demonstrating multiple recurrent strictures.

**Table 2**
Immunologic, medical, and surgical treatment for patients with severe intestinal failure and combined immunodeficiency with TTC7A mutations.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| *TTC7A mutation* | Compound Heterozygous | Compound Heterozygous | Homozygous | Compound Heterozygous | Homozygous | Compound Heterozygous |
| *Immunodeficiency Treatment* | IVIG every 3 weeks | IVIG every 3 weeks | IVIG every 3 weeks | IVIG every 2 weeks | IVIG every 3 weeks | IVIG every 2 weeks |
| *Antibiotic Prophylaxis* | Yes | Yes | Yes | Yes | Yes | Yes |
| *Stem Cell Transplantation* | Yes | Yes | No | No | No | No |
| *Medical Therapy with Leflunomide* | No | No | No | Yes | No | No |
| *Multivisceral Transplantation* | Yes | Listed | Not listed | Not listed | Listed | Yes |
| *Initial Surgical Management* | Diversion, Jejunostomy | Diversion, Jejunostomy | Diversion, Duodenostomy | Pyloric Atresia Resection | Diversion, Jejunostomy | Resections, Ileostomy |
| *Survival* | Yes | No | Yes | Yes | No | Yes |

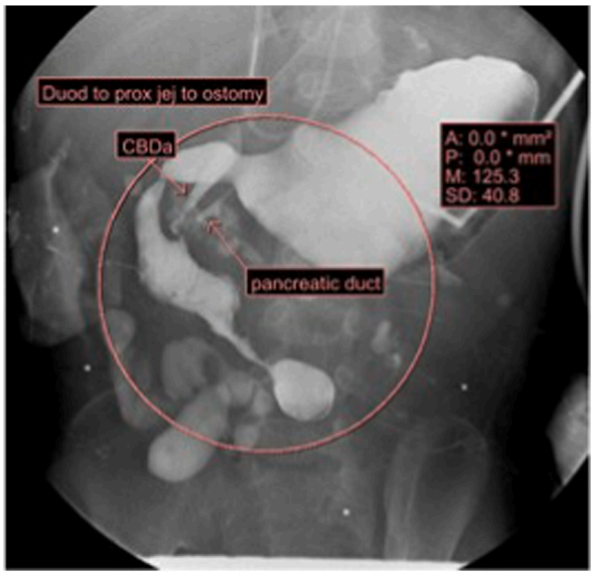


**Fig. 2.** Upper GI series from patient 2 demonstrating intestinal strictures and associated reflux of contrast into the common bile duct and pancreatic duct.

prophylaxis and IVIG therapy were initiated (Table 2). Genetic testing identified a homozygous mutation in the *TTC7A* gene (Table 1). A pyloric web was initially managed with a stent followed by pyloroplasty. Severe bronchopulmonary dysplasia leading to chronic respiratory insufficiency rendered him a poor candidate for bone marrow and multivisceral transplant. At most recent follow up (age 7), he had a WAZ of −0.97, and has remained fully dependent on PN and fish oil-based lipid emulsion with most recent liver evaluation notable for Metavir F2 (Table 1).

### *2.4. Presentation of case 4*

Case 4 is a preterm female born at 34 weeks GA who presented with feeding intolerance secondary to a pyloric atresia. After resection, she continued to have difficulty tolerating enteral nutrition with frequent emesis and diarrhea. Work-up revealed normal contrast studies but grossly abnormal appearing mucosa on endoscopy. Pathology demonstrated epithelial abnormalities including villous atrophy and apoptosis, consistent with congenital enteropathy. She was started on immunosuppression and antimicrobial prophylaxis with mild improvement. Immunologic work-up revealed lymphopenia with IgG and IgM deficiency, but diagnosis remained unclear. Her immunoglobulin deficiencies were thought to be secondary to protein loss due to diarrhea, so she was started on IVIG replacement therapy. Genetic testing identified a compound heterozygous mutation in the *TTC7A* gene, and she was taken off immunosuppression. After this diagnosis was made, she was evaluated for bone marrow transplant. However, it was determined that the risks of transplant outweighed the benefits in her case, due to the mild nature of her phenotype. She was later started on experimental therapy with Leflunomide based on in vitro organoid testing [8] (Table 2). She, at age 4, continues to require PN and combination lipid emulsion (soy, medium chain triglycerides, oleic acid, fish oil) for approximately 90% of her caloric needs (Table 1).

### *2.5. Presentation of case 5*

Case 5 is a full-term male who presented with prenatally diagnosed omphalocele and intestinal obstruction. Several days after birth,

he underwent laparotomy and was found to have pyloric atresia, duodenal atresia, malrotation with volvulus involving the majority of small bowel, and colonic atresia (Fig. 3). A majority of the small bowel was resected, and a gastrostomy tube was placed. A TREC assay was sent demonstrating absent TRECs, which was concerning for SCID. Genetic testing ultimately confirmed a homozygous mutation in the *TTC7A* gene (Table 1). He was listed for bone marrow and multivisceral transplant (Table 2). However, he died at 4 months of age from a cardiac complication following a balloon valvuloplasty procedure for aortic stenosis.

### 2.6. Presentation of case 6

Case 6 is a premature male born 35 weeks GA who presented with bowel obstruction and was found to have multiple intestinal atresias including pyloric atresia, requiring multiple bowel resections and creation of an ileostomy. He was also noted to have CID and was started on IVIG replacement therapy (Table 2). WES identified a compound heterozygous mutation in the *TTC7A* gene (Table 1). He was intially maintained on PN but eventually developed cholestatic liver disease with subsequent liver failure. At 16 months of age, he underwent a combined liver-small bowel transplant, which was complicated by engraftment of donor lymphocytes resulting in severe graft-versus-host disease (GVHD). However, following transplantation, he was able to be weaned from PN and has remained fully enterally autonomous with a WAZ of −1.85 at most recent follow up (age 22, Table 2).

## 3. Discussion

This case series of six patients demonstrates the common clinical features of patients with biallelic *TTC7A* mutations and highlights key management strategies for identifying these complex patients and improving their long-term survival.

It has previously been reported that patients with TTC7A deficiency have widespread atresias affecting the GI tract anywhere from the pylorus to the anus [3]. In this case series, pyloric atresia was a common factor among all six patients with biallelic mutations. However, pyloric atresia in the general population is quite rare, accounting for only 1% of all intestinal atresias with an estimated incidence of 1 in 100,000 live births [9,10]. Thus, if a pyloric web or atresia is identified in an infant, it is important to review results of newborn screening for SCID if available, or to consider evaluation with lymphocyte subsets, because T cell lymphopenia should trigger both an immunologic and a genetic evaluation for *TTC7A* mutations.

For those who survived infancy, the mucosal disease and propensity to re-stenose after initial resection of atretic bowel present ongoing challenges in the management of these patients. Two patients in this series developed recurrent stenosis despite attempts at restoring luminal patency with stricturoplasties and balloon dilation procedures. In addition to pyloric atresia, the other common feature among patients with biallelic *TTC7A* mutations was the presence of mucosal atrophy and epithelial architectural disruption on endoscopy and biopsy, which is thought to be due to loss of apical polarity and apoptosis of intestinal epithelial cells. Recently, the drug Leflunomide has been proposed as a potential therapy in the management of patients with TTC7A deficiency, given its promising results in reducing mucosal apoptosis and restoring gut function in a zebrafish model of TTC7A deficiency as well as in primary patient derived colonoids (from patient 4) [8].

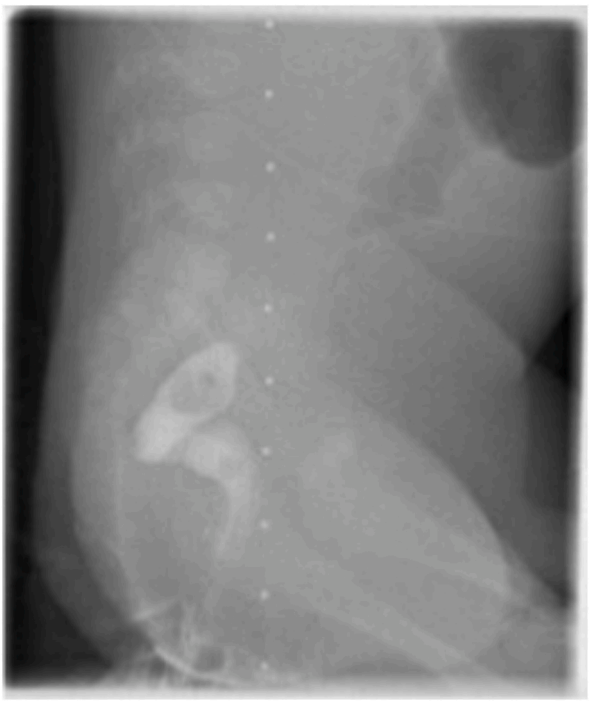

**Fig. 3.** Barium enema from patient 5 showing colonic atresia.

Interestingly, two patients experienced significant recurrent pancreaticobiliary complications. One patient suffered from recurrent pancreatitis while another was treated multiple times for cholangitis. The etiology of their pancreaticobiliary disease is unclear, but in one case an upper GI imaging study demonstrated free reflux of contrast into the biliary tree and pancreatic duct, suggesting a possible vulnerability to ascending inflammatory and infectious processes. Potential mechanisms of such a phenomenon may involve the inherent mucosal dysfunction associated with TTC7A deficiency, as well as possible incompetence of the ampulla of Vater.

All but one patient had MIA requiring multiple bowel resections, which resulted in a median residual bowel length of 15 cm, correlating with a median of 5.8% expected bowel length for the cohort [11]. These patients all received proximal diversion and drainage with a gastrostomy tube, allowing decompression of their stomach and bowel. Notably, this series of patients demonstrated a significantly lower mean pre-transplant citrulline level compared to published norms ($4.65 \pm 2.44$ vs $31.2 \pm 1.6$ micromol/L, $p < 0.001$; Table 1). Fitzgibbons et al. previously identified a threshold citrulline level of greater than or equal to 15 micromol/L to be predictive of reaching PN independence in children with intestinal failure [12]. Based on the low citrulline levels in this series of patients with TTC7A deficiency, it is unlikely that any would attain enteral autonomy without intestinal transplantation.

All four patients with TREC testing available, either by newborn screening for SCID or TREC assay testing postnatally, had results consistent with T cell lymphopenia, and all six were ultimately diagnosed with CID by flow cytometry. The etiology of CID in these patients is hypothesized to be related to the epithelial defects in the thymus caused by the *TTC7A* mutations [13]. Of note, the immunologic manifestations of the CID in each of these cases were not associated with classic opportunistic infections. Initial management of CID in all patients with TTC7A deficiency should include IVIG and antimicrobial prophylaxis, with consideration of stem cell transplantation when appropriate. Three patients in this series were evaluated for stem cell transplant, of whom two underwent successful transplantation. Two others were evaluated for stem cell transplant but were instead continued on IVIG therapy. The decision-making regarding stem cell transplant is complicated and multifactorial. The risks outweighed the potential benefits for several patients in this series, due to liver disease that complicates or contraindicates the use of standard chemotherapy pre-transplant conditioning, concerns about excess toxicity of these agents to the abnormal intestinal epithelium, and ultimately the inability of stem cell transplant to treat the intrinsic intestinal epithelial defects in TTC7A disease. Ideally correction of both the immunodeficiency and the intestinal problems should be pursued in a coordinated or tandem fashion.

The mortality of patients with TTC7A deficiency is quite high and is most commonly due to sepsis or complications from abdominal surgery [4]. Remarkably, four of the six patients in this cohort experienced long-term survival. One patient with severe congenital heart disease died at four months of age, while a second patient succumbed at age seven while awaiting multivisceral transplant. In addition to this case series, there is a single case report of long-term survival in a child with TTC7A deficiency and intestinal failure, whose management included multivisceral transplant with subsequent immune reconstitution after he engrafted T cells from the intestinal donor [14]. In amalgam, these reports highlight the need for integrated multidisciplinary decision making and management of both intestinal failure and CID.

Nutritionally, all patients were initially maintained on hepatoprotective PN, with either fish oil lipid emulsion or combination lipid emulsion (soy, medium chain triglycerides, oleic acid, fish oil) as their lipid source. Those that survived infancy had normal (i.e., greater than $-1$) body mass index (BMI) Z scores (Table 1). The two patients who were continued on PN had normal weight-for-age Z scores at the time of last follow-up, but the two patients who were enterally autonomous following intestinal transplant had weight-for-age Z scores less than $-1$, indicating mild malnutrition (Table 1). This finding reinforces the need for close follow up of these patients, even after weaning from PN.

## 4. Conclusion

The key factors for successful management of this complex clinical syndrome are early identification of the biallelic *TTC7A* mutation and prompt interdisciplinary treatment of the intestinal failure and immunodeficiency. Treatment for the immunodeficiency includes: antimicrobial prophylaxis, IVIG, and potentially stem cell transplant. Management of the intestinal failure involves: hepatoprotective PN, immunomodulators such as Leflunomide, primary repair of atresias if present, and proximal diversion and gastrostomy tube drainage. Definitive surgical treatment may require multivisceral or intestinal transplant, which as demonstrated in two patients in this series, can lead to long-term survival and enteral autonomy.

## Author contributions

All authors attest that they meet the current ICMJE criteria for Authorship.

## Disclosures

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## Informed consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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