

Ureteral fistula manifesting as unexplained ascites during treatment with immunotherapy in POLE-mutated metastatic colorectal cancer: A case report

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Abstract. DNA polymerase ϵ (POLE) proofreading-deficient variants (POLE-pds) are rare in metastatic colorectal cancer (mCRC) but may predict high sensitivity to immune checkpoint inhibitors. Tumors invading the hollow viscera can develop fistulas due to treatment-induced necrosis. However, immunotherapy-associated ureteral fistulas may present atypically. The current study describes the case of a 52-year-old male patient with mCRC harboring the POLE P286R mutation. After second-line therapy failure, the patient received penpulimab plus anlotinib. Following four treatment cycles, the patient developed unexplained ascites and peritoneal thickening, which were initially considered to potentially indicate disease progression or immune-related adverse events. A ureteral tumor fistula was identified 3 months later; the ascites-to-serum creatinine ratio (3.4:1) and resolution after nephrostomy confirmed urinary leakage. Notably, the patient achieved sustained clinical complete remission for >2.5 years without further antitumor therapy. Ureteral fistulas presenting as ascites are a diagnostically challenging complication during treatment with immunotherapy. Early recognition and conservative management via nephrostomy can be effective and patients with POLE-pd mCRC can achieve durable remission despite such complications. Trial registration no. NCT04970914; date of registration, July 21, 2021.

Introduction

DNA polymerase ϵ (POLE) mediates DNA replication and repair (1,2). POLE proofreading-deficient variant (POLE-pd) tumors exhibit an ultra-high tumor mutation burden (TMB) (3,4) and a T-cell-rich microenvironment (4), predicting anti-programmed cell death protein 1 (PD-1) efficacy in mismatch repair-proficient (pMMR) tumors. However, non-proofreading POLE mutations confer no such benefit (4). POLE-pds occur in only 0.6-1.7% of colorectal cancers (CRCs) (4,5).

The present report describes a patient with previously treated metastatic CRC (mCRC) harboring a POLE P286R mutation who achieved a durable complete clinical response (cCR) following treatment with penpulimab (AK105; an anti-PD-1 IgG1 antibody) (6,7) combined with anlotinib (a multi-targeted angiogenesis inhibitor) (8). Notably, during the course of treatment, the patient developed an unusual presentation of a ureteral fistula with persistent and unexplained ascites as the initial symptom. This is a rare complication that is particularly challenging to diagnose and may be easily overlooked in clinical practice. To the best of our knowledge, the current case represents the first description of a ureteral fistula presenting predominantly as ascites, with successful conservative management and >2.5 years of sustained remission.

Case report

A 52-year-old male patient was admitted to Peking Union Medical College Hospital (Beijing, China) in October 2021 due to retroperitoneal lymph node metastasis following right-sided colon cancer resection. The patient had initially undergone laparoscopic radical resection for right colon cancer at Cao County People's Hospital (Weifang, China) in April 2020. Histopathological examination revealed moderately differentiated adenocarcinoma (pT4N0M0) and immunohistochemical analysis confirmed the pMMR status. From May to October 2020, the patient received eight cycles of adjuvant chemotherapy with oxaliplatin combined with capecitabine. During routine follow-up in October 2021, imaging studies identified

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a metastatic lymph node at the anterior aspect of the inferior vena cava, with involvement of the mid-ureter at the level of the L4 vertebral body (Fig. S1A-C).

Next-generation sequencing (NGS) was performed on tumor tissue using a 41-gene panel (catalogue no. LK105; Guangzhou Burning Rock Medical Laboratory Co., Ltd.) on the Illumina NovaSeq 6000 platform (Illumina, Inc.). Clean reads were aligned to the human reference genome GRCh37/hg19. Variants were called using VarDict v1.5.1 (VarDict; <https://github.com/AstraZeneca-NGS/VarDict>) and annotated using BrasAnnotation v4.3.0 (Guangzhou Burning Rock Medical Laboratory Co., Ltd.). The assay achieved a mean sequencing depth of $\geq 500\times$, with a Q30 ratio of $\geq 80\%$. The POLE P286R mutation was identified along with 29 additional somatic mutations, while microsatellite stability (MSS) was confirmed. Detailed NGS methodology is provided in Tables SI and SII and the Supplementary material.

From October to December 2021, the patient received four cycles of 5-fluorouracil, leucovorin and irinotecan combined with bevacizumab. However, restaging imaging revealed disease progression (Fig. S1D), accompanied by mild dilation of the right renal pelvis and proximal ureter, suggesting possible ureteral obstruction secondary to tumor progression.

The patient was subsequently enrolled in a clinical trial (NCT04970914) at Peking Union Medical College Hospital in March 2022. The patient received two cycles of penpulimab (200 mg on day 1 of each 21-day cycle) plus anlotinib (12 mg daily on days 1-14) overall in March and April 2022. Restaging imaging after the second cycle demonstrated stable disease (Fig. 1A and B). The third cycle was administered later in April 2022. In early May 2022, the patient developed transient, self-resolving mild abdominal pain and dysuria without an identifiable cause. Subsequent laboratory tests revealed mildly elevated serum creatinine levels (130 $\mu\text{mol/l}$ in mid-May and 127 $\mu\text{mol/l}$ in late May; reference range, 59-104 $\mu\text{mol/l}$), although urinalysis was unremarkable. Renal ultrasound demonstrated persistent mild dilation of the right renal pelvis and proximal ureter (data not shown). The fourth treatment cycle was administered as scheduled in May 2022. By early June 2022, renal function had normalized, but ultrasound revealed new-onset mild right hydronephrosis and moderate ascites (data not shown; findings extracted from the patient's medical file). In early June 2022, the patient reported abdominal distension, prompting therapeutic abdominal paracentesis. The ascitic fluid was initially hemorrhagic and became light yellow and clear 2 days later. Cytological examination of the ascites was negative for malignancy on three separate occasions. A CT scan in mid-June 2022 confirmed moderate ascites with omental thickening (Fig. 1C and D); the previously noted mild hydronephrosis showed no significant worsening compared with prior imaging. At that time, despite a slightly smaller metastatic lymph node, the ascites remained unexplained; anlotinib was withheld for one cycle, while penpulimab was continued given the known sensitivity of POLE-pd tumors to immunotherapy. The fifth cycle of penpulimab monotherapy was administered in late June 2022, but persistent unexplained ascites requiring recurrent drainage and delay of antitumor treatment led to the patient's study withdrawal in July 2022.

During routine follow-up CT in early September 2022, a fistula between the tumor and right ureter was identified. The fistula formed a well-defined cystic mass (Fig. 2A), which was subsequently confirmed by positron emission tomography (PET)-CT. To manage this complication, drainage tubes were inserted into both the fistula sac and peritoneal cavity in mid-October 2022. Biochemical analysis revealed that the creatinine levels of the fistula sac and ascites were 3,282/l and 232 $\mu\text{mol/l}$, respectively. The corresponding serum creatinine level at that time was 69 $\mu\text{mol/l}$, yielding an ascites-to-serum creatinine ratio of 3.4:1, which strongly suggested urinary leakage. Following failed ureteral stent implantation, a right nephrostomy was performed two days later. The patient's abdominal distension was completely resolved, and both the fistula sac and ascites volume were markedly reduced 3 weeks later (Fig. 2B and C), which prompted removal of the drainage tubes. A CT scan in late March 2023 showed resolution of omental fibrous density (Fig. S2A-D), minimal residual ascites and reduction of the fistula-associated cyst to 2x1 cm. The nephrostomy tube was successfully removed in mid-May 2023.

A detailed timeline of all major clinical events, including surgery, systemic therapies, fistula diagnosis and follow-up, is shown in Fig. 3. During regular follow-ups every 3-6 months, the patient maintained normal tumor markers with no evidence of disease recurrence on CT scans. PET-CT in June 2024 revealed no active lesions (Fig. S3A-C). Based on these findings, including complete radiographic resolution, normal tumor markers, absence of symptoms and sustained remission for >12 months without any antitumor therapy, the patient was assessed as having achieved cCR. As of the submission of the manuscript, the last CT scan in June 2025 confirmed no evidence of tumor and a residual small cyst (Fig. 2D). No further antitumor therapy was administered, and no additional intervention was required for the residual cyst or the urinary tract. Renal function remained normal during follow-up. The patient remained in good general condition throughout the surveillance period.

Discussion

POLE exerts exonuclease activity via its proofreading domain and deletes mispaired bases inserted during DNA replication. POLE-pds lead to the accumulation of missense and nonsense mutations, typically manifesting as an ultra-hypermuted phenotype with a TMB exceeding 100 mutations/megabase (3,9). Such extreme mutagenesis generates abundant neoantigens, which may explain the enhanced clinical responsiveness to immune checkpoint inhibitors (ICIs) observed in POLE-pd tumors (10,11). The exonuclease domain contains several well-characterized mutational hotspots that impair the proofreading capacity, with P286R representing one of the most frequently documented pathogenic variants in this critical functional domain (4,9).

POLE-pds exhibit low prevalence in mCRC, occurring in <1% of cases (12). This rarity may reflect the favorable prognosis associated with these tumors following primary resection (13). Large-scale genomic analyses have revealed that among 9,136 CRC specimens, only 2.4% harbored alterations in either POLE or polymerases δ (POLD1), with a mere

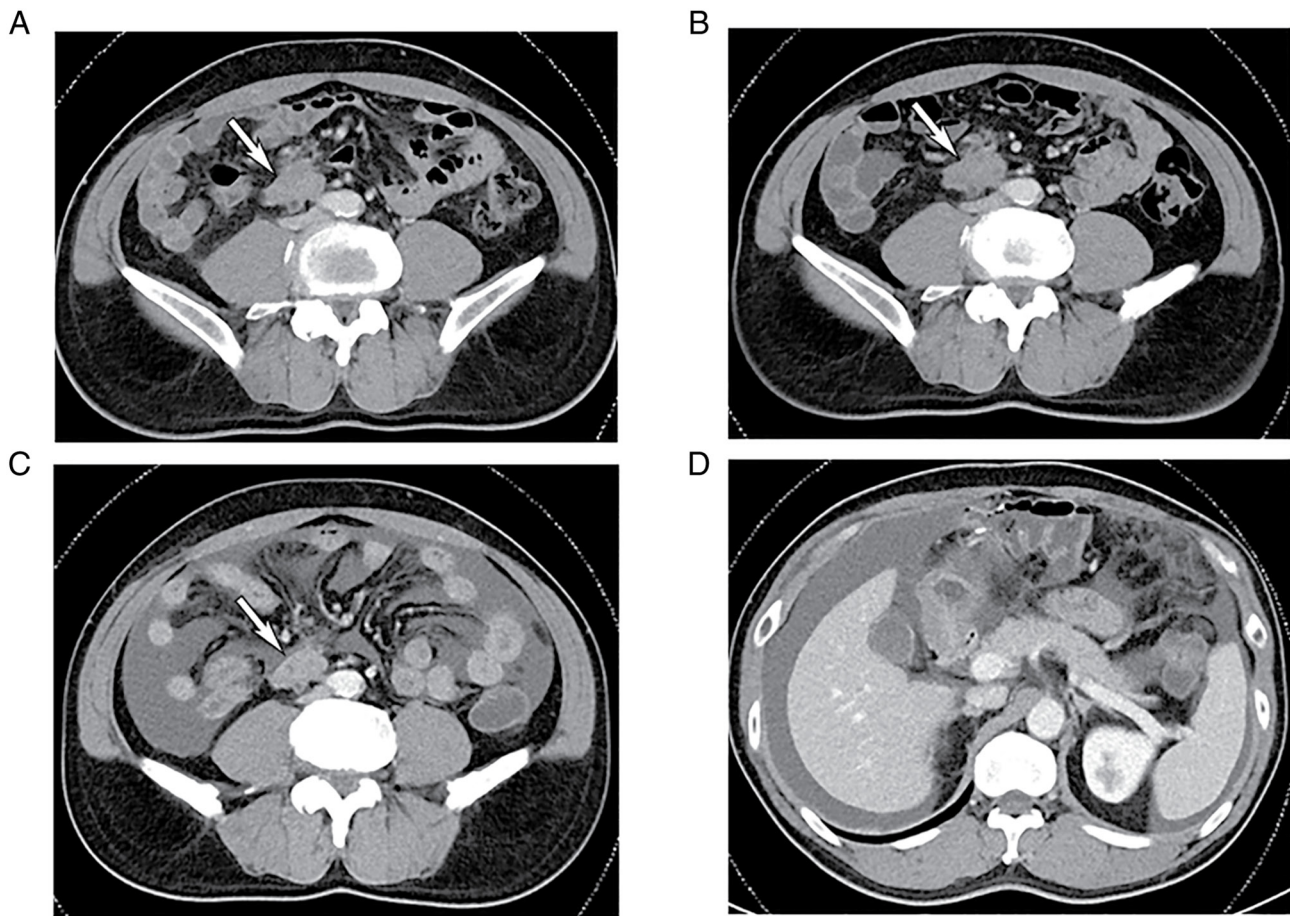


Figure 1. Abdominal CT imaging during the treatment with penpulimab and anlotinib. (A) Baseline CT (March 2022) indicated a metastatic lymph node (white arrow) at the anterior aspect of the inferior vena cava involving the mid-ureter. (B) Stable disease of the metastatic lymph node (white arrow) after two cycles of treatment (April 2022). (C) CT scans in June 2022 (after the fourth cycle) showing that the metastatic lymph node (white arrow) became slightly smaller. (D) CT scans in June 2022 showing moderate ascites and omental thickening.

0.4% exhibiting the characteristic ultra-hypermutated phenotype (14). Notably, patients with POLE-pd CRC exhibited a markedly elevated TMB compared with those with microsatellite instability-high (MSI-H) tumors or POLE variants outside the exonuclease domain (15).

Accumulating clinical evidence suggests that patients with CRC with POLE-pds exhibit excellent responses to ICIs. The first documented case was reported in 2017 and the patient with treatment-refractory mCRC with the MSS phenotype and POLE mutation exhibited a remarkable response to pembrolizumab (16). Subsequent case reports further supported these findings, demonstrating excellent immunotherapy outcomes in patients with pathogenic POLE mutations (17,18). In 2022, Wen *et al* (15) reported 4 patients with CRC with liver metastasis who received toripalimab or sintilimab combined with chemotherapy (with or without bevacizumab) after POLE exonuclease domain mutations were detected. All 4 patients achieved a pathological complete response after surgery despite showing only a partial response on radiological evaluation. Recent larger studies have further validated these findings. A global study of 27 patients with mCRC with POLE/POLD1 mutations leading to proofreading deficiency revealed superior response rates to ICIs and survival outcomes after ICI treatment compared with those of MSI-H patients (3). In a retrospective

analysis (19), 22 consecutive patients with locally advanced CRC with MSI-H or POLE-mutated bulky tumors (>8 cm) received neoadjuvant PD-1 blockade. Among the 2 patients with POLE mutations, 1 each achieved pathological or clinical complete remission.

In the present case, the combination of anti-PD-1 therapy with anlotinib (a multi-target tyrosine kinase inhibitor targeting VEGFR2/3, fibroblast growth factor receptor 1-4, platelet-derived growth factor receptor α/β , c-Kit and Ret) (20) may have produced synergistic effects (21), leading to durable complete remission for >2.5 years after treatment cessation. However, this profound response was accompanied by an unusual complication that posed significant diagnostic and therapeutic challenges.

The development of the ureteral fistula in the present patient is best understood as a multi-factorial event rather than a direct and sole effect of immunotherapy. First, the metastatic lesion already directly involved the mid-ureter at baseline, structurally compromising the ureteral wall. Second, the profound and rapid tumor necrosis induced by effective immunotherapy disrupted the tumor-ureteral interface (22). Third, the anti-angiogenic effect of anlotinib may have impaired local tissue repair and wound healing, facilitating fistula formation (23,24). Therefore, while immunotherapy was the primary driver of tumor regression, the fistula was likely the

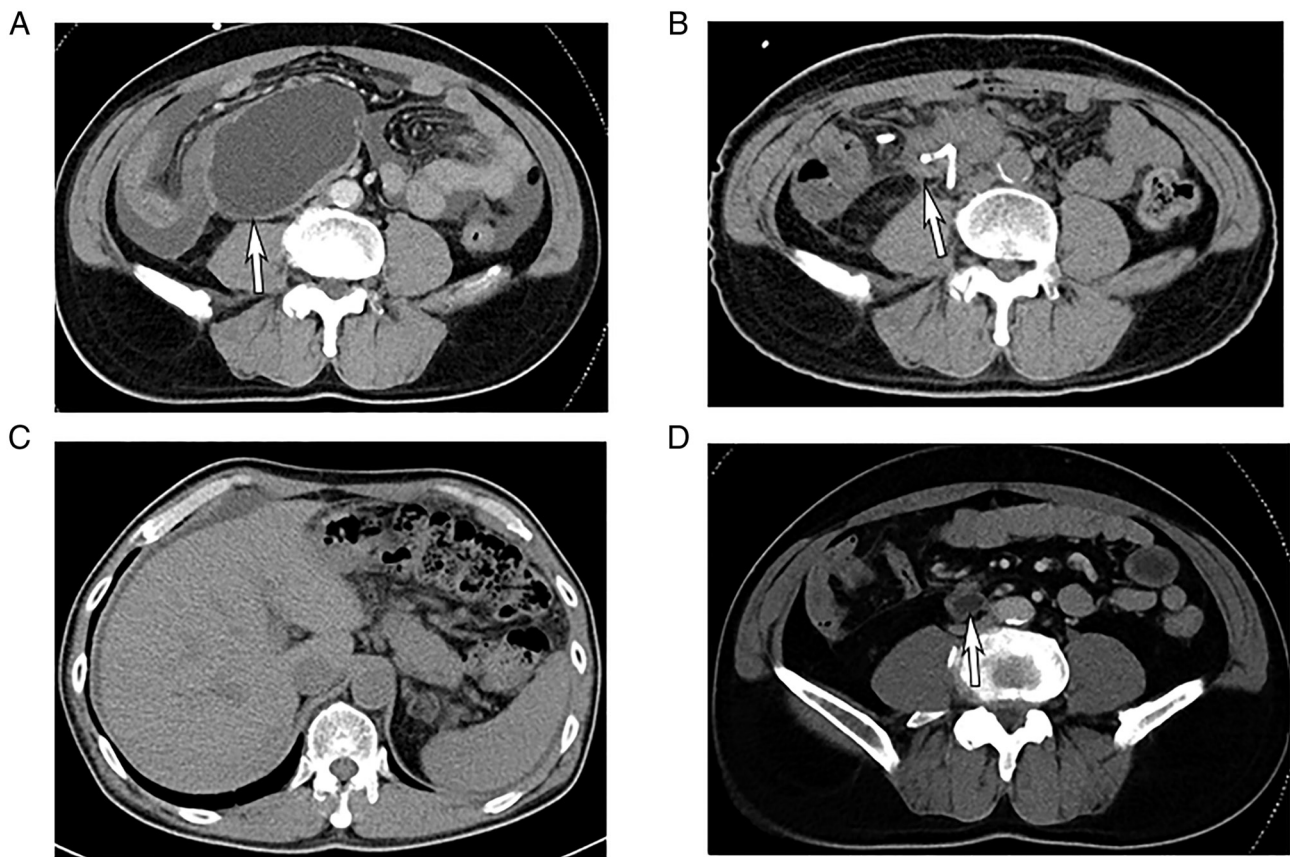


Figure 2. Manifestations and outcomes of the ureteral fistula. (A) A fistula between the tumor and right ureter was identified and the fistula formed a well-defined cystic mass (white arrow) in September 2022. (B) The fistula sac (white arrow) was markedly reduced 3 weeks after drainage of the fistula sac and right nephrostomy (November 2022). (C) The ascites volume was markedly reduced (November 2022). (D) A small cyst (white arrow) remained in the previously metastatic lymph node area in June 2025.

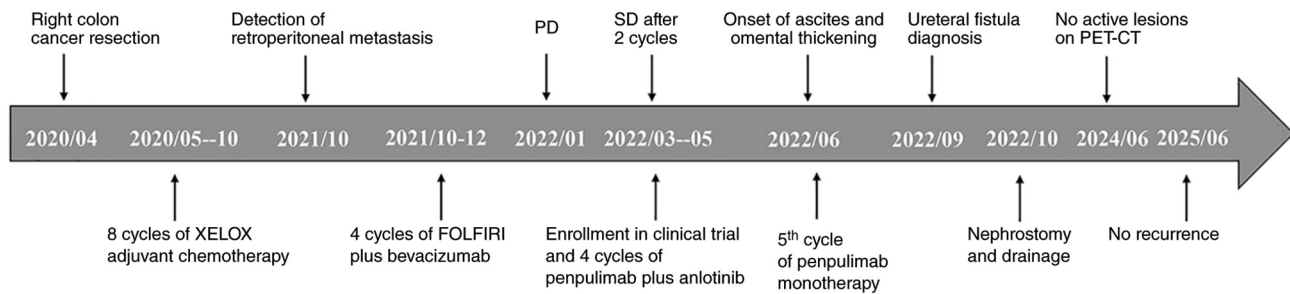


Figure 3. Timeline of major clinical events. Dates are presented as year/month or year/month ranges (e.g., 2020/05–10 denotes May to October 2020). PET, positron emission tomography; PD, progressive disease; SD, stable disease; XELOX, oxaliplatin and capecitabine; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan.

result of combined contributions from baseline invasion, treatment response and anti-angiogenic therapy.

The diagnostic chain for urinary ascites in the present case is instructive. The patient exhibited minimal urinary tract symptoms, and early imaging studies, including ultrasound and a CT scan, failed to provide evidence of fistula formation. Initially, ascites and peritoneal thickening raised suspicion of peritoneal carcinomatosis (ruled out by three negative cytologies) or rare immune-related serositis (unlikely given the poor response to treatment interruption). The key diagnostic evidence included: i) Elevated creatinine levels in the fistula sac (3,282 $\mu\text{mol/l}$)

and ascites (232 $\mu\text{mol/l}$), with a serum creatinine level of 69 $\mu\text{mol/l}$, yielding an ascites-to-serum ratio of 3.4:1, which was highly suggestive of urinary leakage; ii) delayed CT imaging that eventually visualized the distinct fistula sac; and iii) definitive therapeutic confirmation, including complete resolution of ascites following nephrostomy and fistula sac drainage. Early imaging missed the fistula, potentially because it was initially small and collapsed, with urine leaking directly into the peritoneal cavity rather than forming a localized collection; the fistulous tract only became radiologically detectable as it matured into a defined cystic sac over time.

The choice of conservative management over surgical repair was deliberate. Surgical intervention was considered high-risk due to the following: i) Active immunotherapy and anti-angiogenic effects potentially impairing wound healing; ii) effective symptomatic control with drainage; and iii) achievement of tumor remission, which made fistula repair unnecessary if the urinary leak could be controlled. Nephrostomy combined with continuous fistula sac drainage proved to be an effective and less morbid approach, and this strategy may serve as a reference for similar cases.

This rare complication, while presenting significant diagnostic and therapeutic challenges, paradoxically reflects the profound depth of the antitumor response induced by immunotherapy. The occurrence of fistula formation in the present case aligns with previous reports of fistula formation in rapidly responding tumors (22,25). The patient's sustained remission for >2.5 years without further therapy supports the growing recognition that POLE-mutated CRC represents a distinct molecular subtype with exceptional sensitivity to ICIs (3,15).

In conclusion, mCRC harboring a POLE-pd is highly sensitive to immunotherapy. Rapid tumor regression after immunotherapy may lead to the formation of a fistula between the tumor and the adjacent organs. Ureteral fistulas presenting with ascites as the primary symptom are rare and diagnostically challenging. With the increasing clinical application of immunotherapy, awareness of such rare complications is necessary for timely diagnosis. Successful conservative management via nephrostomy and drainage may provide a clinically actionable approach for similar cases of ureteral fistulas.

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Availability of data and materials

The raw sequencing data generated in the present study may be found in the China National Center for Bioinformation (CNCB-NGDC) under BioProject accession no. PRJCA073069 or at the following URL: <https://ngdc.cncb.ac.cn/omix/preview/SfmOFgG7WE>.

Authors' contributions

JZ designed and supervised the study. JZ and XGo analyzed patient data and wrote the manuscript. XGa contributed to the acquisition of the medical images, and the analysis and interpretation of the imaging data, and critically revised the manuscript. All authors have read and approved the final version of the manuscript. JZ, XGo and XGa confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Human Research Ethics Committee of Peking Union Medical College Hospital

(Beijing, China; approval no. HS-2986B) and the patient provided written informed consent to participate in the clinical trial.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of all case information and medical images included in the present article.

Competing interests

The authors declare that they have no competing interests.

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