Anlotinib plus tislelizumab for recurrent metastatic pancreas ductal adenocarcinoma with germline BRCA2 mutation: A case report

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Abstract. While combined immunotherapy and anti-angiogenic therapy have demonstrated efficacy in renal cell carcinoma, non-small cell lung cancer and hepatocellular carcinoma, the efficacy of first-line treatment for pancreatic ductal adenocarcinoma (PDAC) with germline BRCA2 mutation remains unproven. We described a BRCA2-mutated patient with PDAC who presented with posterior cardiac metastasis 8 months after surgery. After receiving four cycles of anlotinib combined with tislelizumab, abdominal CT scans indicated a complete response. The patient sustained this response for over 14 months on the combination regimen, with no reported adverse events. In conclusion, the combination of tislelizumab and anlotinib may offer a viable therapeutic option for recurrent metastatic BRCA2-mutated PDAC.

Introduction

In 2020, pancreatic cancer (PC) resulted in 496,000 new cases and 466,000 mortalities, with pancreatic ductal adenocarcinoma (PDAC) as the predominant type (1,2). A majority of patients with PC are diagnosed at an advanced stage, therefore, only 20% are eligible for radical surgical resection (3). However, despite surgery, ~90% of patients experience disease recurrence within 7-9 months, leading to a 5-year overall survival (OS) rate <10% (4). The growing adoption of genetic testing has enabled the implementation of precision medicine (5). BRCA1, BRCA2 or both (BRCA) mutations are present in 5-10% of familial patients with PDAC and ~3% of sporadic ones (6). Such mutations can induce homologous recombination deficiency (HRD), impeding the efficient repair of double-stranded DNA breaks (7). The conventional treatment for metastatic PDAC with germline BRCA mutations is platinum-based chemotherapy coupled with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor maintenance therapy (5,8-10). While this regimen can enhance survival metrics, a long-lasting clinical response remains elusive, and its toxicity is noteworthy. Exploring innovative therapeutic approaches is thus essential, particularly for patients with PDAC carrying BRCA2 mutations.

Research suggests that BRCA2 mutations may boost tumor cell immunogenicity and enhance responsiveness to immune checkpoint inhibitors (ICIs) (11). Moreover, a retrospective study of metastatic pancreatic or biliary cancer with HRD has demonstrated significant clinical activity of ipilimumab/nivolumab with an objective response rate (ORR) of 42% and a disease control rate (DCR) of 58% (12). However, given the limited sample size of the study, the efficacy of ipilimumab/nivolumab for BRCA2-mutated metastatic PC requires further validation. There's growing evidence that anti-angiogenic drugs can modify the immune microenvironment of the tumor, potentially amplifying immunotherapy benefits (13). Such synergy has been observed in renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC) (14). Additionally, several instances highlight the potential of integrating anti-angiogenic drugs with ICIs in sequential treatments for PC (15,16). Yet, the effectiveness of this combined approach as an initial treatment for PDAC with germline BRCA2 mutations is still uncertain.

The present study presented a case of a patient with BRCA2-mutated PDAC who manifested metastasis in the posterior cardia at 8 months after surgery. The combined therapy of programmed cell death protein 1 (PD-1) inhibitor, tislelizumab, with the anti-angiogenic agent, anlotinib, exhibited notable efficacy in this patient. The patient provided written informed consent for the publication of case information and accompanying images.

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Case report

A 68-year-old male with no family history presented to the First Affiliated Hospital of Nanchang University (Jiangxi, China) in August 2021, complaining of epigastric pain. An abdominal computed tomography (CT) showed a space-occupying lesion in the body of the pancreas. Enhanced CT scans of the chest and pelvis showed no abnormalities. Preoperative carbohydrate antigen 19-9 (CA199) levels were significantly elevated at 798.7 U/ml (normal range, 0-27 U/ml). Given the confined nature of the lesion and the absence of distant metastasis, proceeding with surgical intervention was deemed appropriate. Subsequently, the patient underwent laparoscopic radical pancreatic body-tail resection and splenectomy. The postoperative pathology confirmed a diagnosis of moderately differentiated ductal adenocarcinoma (pT3N0M0) (Fig. 1). The degrees of surgical resection in patients are mainly divided into three parts: Complete resection of the tumor (R0), microscopic residual (R1) and visual residual of the tumor (R2), respectively. The present study mainly adopted the presence or absence of tumor infiltration within 1 mm from the cutting edge as the criterion for judging the R0 or R1 resection of the tumor (17,18). Tumor cells are resected as R1 if they are found within 1 mm of the tip of the tissue; if no tumor cells are found, it is resected as R0. R2 indicates residual tumors visible at the surgical margins (positive margins). The patient in the present case had undergone laparoscopic radical pancreatic body-tail resection and splenectomy, which was considered a R0 resection in conjunction with the postoperative pathological results.

After surgery, the patient declined chemotherapy and other treatments and asked for routine follow-up to monitor the lesion. By May 2022, the patient progressed with the development of a posterior cardiac annular nodule (1.7x1.3 cm) (Fig. 2A) with CA199, which was 35.73 U/ml (Fig. 3). Despite the presence of new lesions, the patient was merely under observation without receiving any treatment. A subsequent upper abdominal CT in August 2022 showed that the nodule had grown to 2.3x2.8 cm (Fig. 2B), and his CA199 level spiked to 124.8 U/ml (Fig. 3). Consequently, the patient was diagnosed with recurrent metastatic PDAC and had an Eastern Cooperative Oncology Group (ECOG) score of 1 (19).

To uncover actionable mutations in the patient, the present study conducted next-generation sequencing (NGS) on both the surgical tissues and blood samples. The analysis identified a BRCA2 mutation, microsatellite stability (MSS), a tumor mutational burden (TMB) of 5.76 Muts/Mb and PD-L1 negativity. As per the 2022 Guidelines of the Chinese Society of Clinical Oncology (CSCO) for Pancreatic Cancer and the NCCN Guidelines for Pancreatic Adenocarcinoma, Version 2, 2023, the recommended course of action was platinum-based chemotherapy (20). However, due to concerns about the adverse effects of chemotherapy, the patient, in consultation with his family, opted against this treatment.

In August 2022 the patient was initiated on a treatment regimen comprising of anlotinib (10 mg, days 1-14; 7 days off; 21-day cycle) and tislelizumab (200 mg, day 1; 20 days off; 21-day cycle). Following four cycles of combination therapy, the patient achieved a complete response (CR), with total tumor disappearance (Fig. 2C). To prevent tumor recurrence, the patient continued this regimen without any treatment-related adverse effects. At the latest follow-up in November 2023, the patient remains on this regimen. Abdominal CT scans continue to indicate CR with a progression-free survival (PFS) duration of 14 months (Fig. 2D).

Discussion

PDAC remains a highly aggressive and devastating disease, typically characterized by a median OS of <13 months in metastatic patients (21). Posterior cardiac invasion is considered a manifestation of peritoneal metastasis, rendering surgical resection not recommended. Consequently, systemic chemotherapy is the established first-line approach for metastatic PDAC (22).

In the present case, the application of NGS testing on the blood and archived specimens of the patient revealed the presence of a BRCA2 mutation, along with negative PD-L1 expression and a low TMB and MSS. The BRCA gene is responsible for encoding proteins involved in homologous recombination repair of double-stranded DNA breaks (23). Consequently, PDAC featuring a germline BRCA mutation exhibits sensitivity to platinum and PARP inhibitors (24,25). The POLO study investigated the efficacy of maintenance olaparib in patients with platinum-sensitive metastatic PC who carried germline BRCA1 or BRCA2 mutations (10). The results showed that maintenance olaparib significantly extends PFS compared with the placebo (median, 7.4 months vs. 3.8 months; P=0.004) (10). However, there was no significant difference in median OS between the two groups (18.9 months vs. 18.1 months; P=0.68) (10). Moreover, in this current case, the patient and his family adamantly declined chemotherapy due to the prohibitive cost of the procedure. Hence, it is imperative to explore alternative chemotherapy-free treatment modalities, aiming to provide enhanced survival prospects for individuals with PDAC.

In recent years, significant attention has been dedicated to the research and development of anti-angiogenic drugs for managing PC. A phase III clinical trial has demonstrated the superiority of combining erlotinib with gemcitabine compared with gemcitabine alone, as it leads to notable improvements in both OS and PFS in patients with locally advanced or metastatic PC (26). However, it is noteworthy that various other anti-angiogenic drug combinations with gemcitabine have not yielded favorable outcomes concerning OS in PC patients (27-34). These findings suggest that the utilization of anti-angiogenic drugs in conjunction with gemcitabine may have some inherent limitations in extending the OS of PC patients. Therefore, there is a pressing need to explore a new anti-angiogenic drug to improve the efficacy of PC treatment.

Anlotinib is a novel multi-targeted tyrosine kinase inhibitor renowned for its capacity to impede both tumor angiogenesis and cell proliferation (35). This therapeutic agent exhibits a broad spectrum of inhibitory effects on various critical targets, encompassing receptor tyrosine kinases such as vascular endothelial growth factor receptor 1 to 3, epidermal growth factor receptor (EGFR), fibroblast growth factor receptor 1 to 4, platelet-derived growth factor

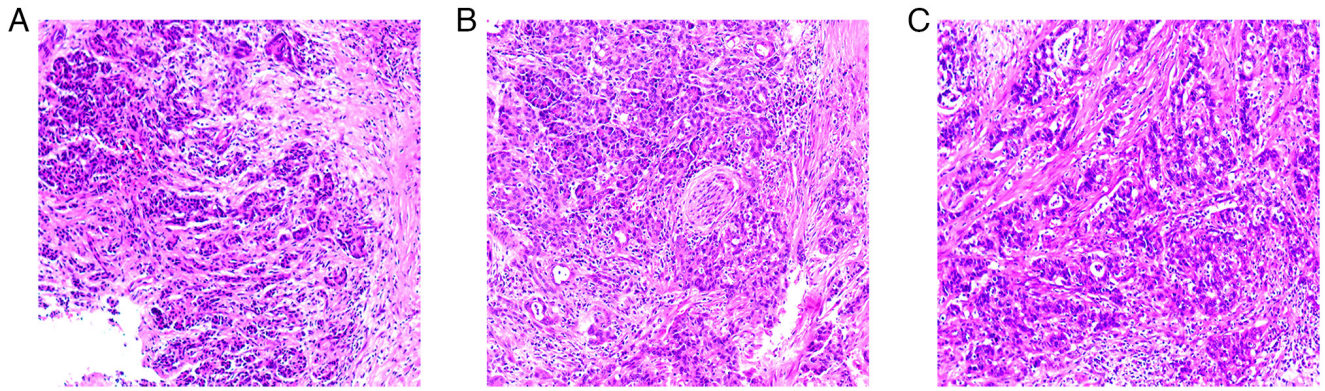

Figure 1. Hematoxylin and eosin staining revealed irregular cancerous glands arranged in a crowded and disorganized manner, infiltrating the pancreatic parenchyma. The nuclei of glandular epithelial cells appeared large and deeply stained, exhibiting obvious pleomorphism and undergoing visible nuclear fission. Additionally, there was a significant presence of peripheral mesenchymal fibroplasia, along with the observed invasion of vasculature and nerve structures. Images were obtained at (A and B) x100 and (C) x200 magnification.

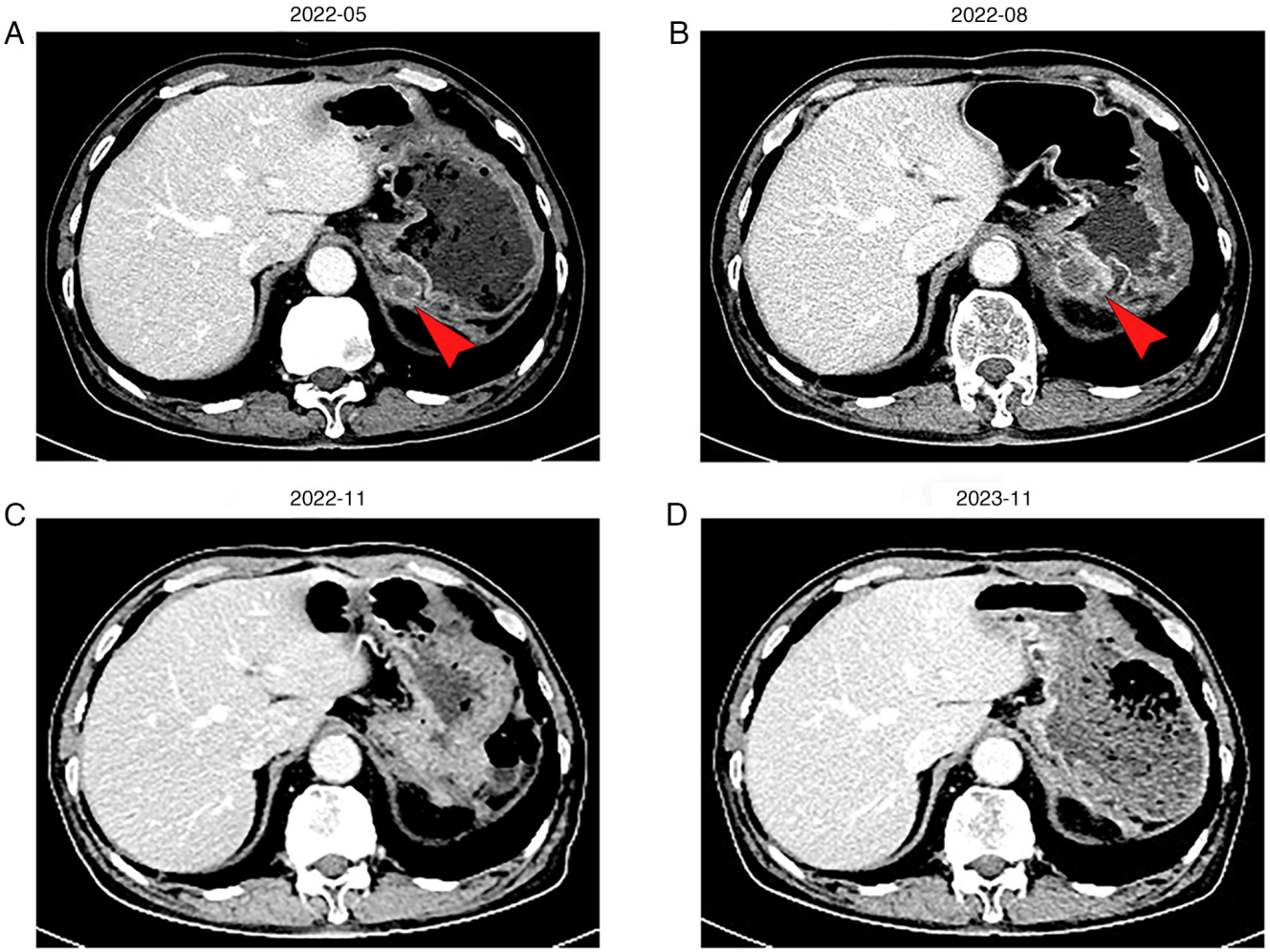

Figure 2. CT scan images following recurring metastasis, the red arrow denotes the posterior cardiac lesion location. (A) The initial recurrent CT examination showed a mass behind the cardia, ~1.7x1.3 cm. (B) On follow-up for 3 months, the posterior cardia mass was enlarged compared with the previous one, about 2.3x2.8 cm. (C) After four cycles of combination therapy, the lesion in the posterior cardia had disappeared. (D) After 20 cycles of this combination therapy, no tumor relapse was observed. CT, computed tomography.

receptors α and β, stem cell factor receptors and c-kit (36). Clinical studies have shown that anlotinib has promising efficacy in the treatment of advanced NSCLC, small cell lung cancer, soft tissue sarcoma (STS), advanced thyroid carcinoma and metastatic RCC (37,38). Moreover, its potential role in the context of PC has garnered substantial attention. Yang *et al* found that anlotinib can induce the apoptosis of pancreatic cells both *in vitro* and *in vivo*

Table I. Clinical study of pancreatic cancer with BRCA2 or BRCA1/2 mutations.

Case	Cancer type	Mutations	Cancer stage	Lines[a]	Current treatments	PFS (m)	OS (m)	(Refs.)
26	PDAC	germline BRCA1, BRCA2 or PALB2 mutation	Locally advanced/ metastatic	First or multiple	Platinum-based therapy	10.1	24.6	(7)
42	PC	BRCA1, BRCA2, or PALB2	Locally advanced/ metastatic	First	Maintenance rucaparib	13.1	23.5	(9)
154	Pancreatic adenocarcinoma	germline BRCA1 or BRCA2 mutation	Metastatic	First	Maintenance olaparib	7.4	18.9	(10)
1	PC	BRCA2 mutation	pT3N1M0	First	Gemcitabine plus iniparib neoadjuvant therapy followed by surgery	32	-	(57)
298	Ovarian cancer, breast cancer, PC, prostate cancer	Germline BRCA1/2 mutation	Advanced solid tumor	Multiple	Olaparib	4.6[b]	9.8[b]	(58)
12	Pancreatic Adenocarcinoma	DNA Damage Repair Gene Mutations	Metastatic	First	FOLFIRINOX[c]	-	14	(59)
-	Solid cancers	Homologous repair genes	-	-	Absence of progression after 6 weeks of olaparib, followed by 4 months of treatment with durva-lumab + tremelimumab, then durvalumab alone for maintenance treatment	-	-	(60)

[a]Number of current treatment regimens. [b]OS and PFS in patients with pancreatic cancer. [c]Including oxaliplatin, irinotecan, fluorouracil and calcium folinate. M, months; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma.

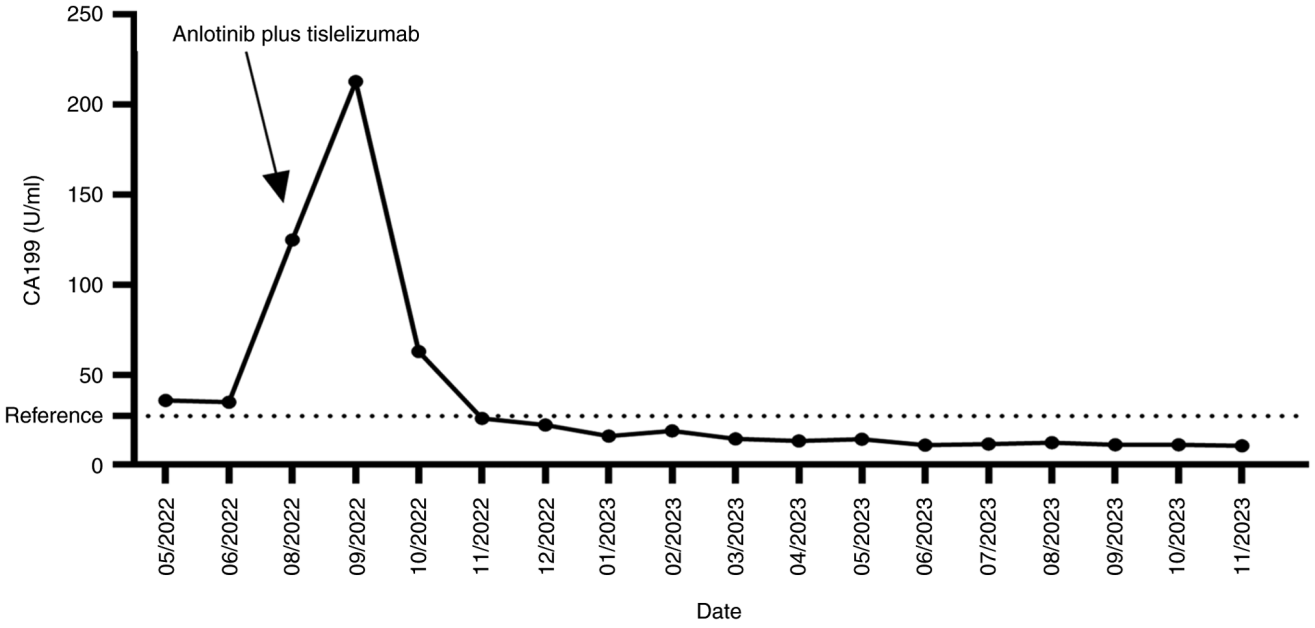

Figure 3. Changes in serum CA199 marker levels after recurrence.

by generating reactive oxygen species (39). Additionally, Zhang *et al* have demonstrated that anlotinib possesses the capacity to inhibit ribosomes within pancreatic cancer cells, thereby modulating various cellular functions, including the cell cycle, RNA metabolism and lysosome (40). In a retrospective study, the combination of anlotinib and nab-paclitaxel/gemcitabine showed a significant improvement in both PFS (5 months vs. 2.7 months, P=0.0220) and OS (9 months vs. 6 months, P=0.0060) in patients with unresectable or metastatic PDAC when compared with albumin-bound paclitaxel/gemcitabine (37). This treatment also maintains favorable tolerability profiles (37). Therefore, anlotinib is expected to be a feasible treatment modality for patients with locally advanced and metastatic PC.

Immunotherapy has revolutionized the treatment of various tumors (41). Recent years have witnessed a notable surge in investigations into ICIs for the treatment of metastatic PC. Several studies have yielded compelling evidence suggesting that combining ICIs with chemotherapy holds promise for enhancing survival outcomes in patients with advanced PC (42-44). However, it is worth noting that, except for high microsatellite instability (MSI-H) or DNA mismatch repair (dMMR), the outcomes of immunotherapy monotherapy or dual-agent immunotherapy in the context of advanced PC have often been underwhelming (45-50). In the present case, the patient was diagnosed with a BRCA2 mutation. A preclinical study has illuminated that BRCA2 mutations can remodel the tumor microenvironment by fostering the enrichment of various immune cell populations, including T cells, natural killer cells, macrophages, and dendritic cells (11). This, in turn, augments the antitumor activity of ICIs (11). However, the patient in the present case had several features that were unresponsive to ICIs, such as negative PD-L1 expression, and low TMB and MSS. Consequently, it is conceivable that immunotherapy alone may offer limited efficacy in this particular scenario.

Emerging research has shed light on the potential immunostimulatory effects of anti-angiogenic drugs and their capacity for synergistic antitumor action when combined with ICIs (51-56). One notable example is the IMPOWER-150 study, which has demonstrated that the addition of atezolizumab to bevacizumab, in combination with chemotherapy as a first-line treatment for metastatic NSCLC, leads to improved clinical outcomes for patients, irrespective of their PD-L1 expression status or the presence of EGFR or ALK mutations (52). In addition, Kang *et al* reported a case in which the combination of pembrolizumab and anlotinib exhibits substantial antitumor activity in PC (16). Similarly, Wang *et al* documented a long-term partial response and favorable tolerability in a 41-year-old patient with PDAC with KRAS G12V mutation and liver metastasis who received the combination of anlotinib with PD-1 inhibitor plus chemotherapy (15). Building upon these insights, the present study sought to explore the potential benefits of combining tislelizumab with anlotinib in the treatment of PC, specifically focusing on patients with metastatic BRCA2 mutated PDAC. Following the administration of four treatment cycles, the response of the patient to therapy was evaluated as CR, and this efficacy persisted for a duration exceeding 14 months. Clinical studies related to PC with BRCA2 or BRCA1/2 mutations are summarized in Table I.

In conclusion, the current study presented a novel and efficacious combination therapy involving immuno- and anti-angiogenic drugs for the treatment of patients with recurrent and metastatic PDAC and BRCA2 mutations. This innovative treatment approach holds promise for diversifying the therapeutic options available to patients with recurrent and metastatic PDAC and BRCA2 mutations, particularly for individuals who either decline or are unable to tolerate conventional chemotherapy. Nonetheless, it is imperative to emphasize that rigorous and extensive clinical trials are still

indispensable to substantiate its efficacy and safety, thereby advancing its adoption in clinical practice.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SP and ZL contributed to the conceptualization and design of the study, the collection of clinical information and the drafting of the manuscript. HH, XZ, JC, XD and FW obtained CT and hematoxylin and eosin staining images, and analyzed patient data. LC was responsible for formulating the patient's treatment plan. LC and HH contributed to critical revisions of the intellectual content. SP and ZL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived due to the type of the study. Written informed consent was obtained from the patient.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this paper and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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