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TUMOR DISAPPEARANCE ON POSITRON EMISSION TOMOGRAPHY COMPUTED TOMOGRAPHY AFTER S-1 TREATMENT FOR POSTOPERATIVE LOCAL RECURRENCE OF GALLBLADDER CANCER

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ABSTRACT – *Objective:* Gallbladder cancer (GBC) typically follows an aggressive course with the standard of care for advanced disease; complete responses are rarely encountered. We report a case in which tumor disappearance on positron emission tomography computed tomography (PET-CT) was treated with S-1 as the second-line treatment for local recurrence of GBC after gemcitabine (GEM) plus cisplatin (CDDP) (GC) combination therapy.

Case presentation: A 69-year-old woman was referred to our hospital with complaints of right hypochondrial pain. Based on ultrasound, CT, and magnetic resonance imaging (MRI) findings, we diagnosed patient with suspected GBC.

Results: We performed the resection of the gallbladder base, partial resection of the transverse colon, and partial resection of the stomach for GBC. At four months after the surgery, PET-CT showed local recurrence. First-line chemotherapy with GC therapy was initiated. After 9 courses, PET-CT showed increased local recurrence. We concluded that GC treatment was ineffective. Second-line chemotherapy with S-1 was initiated for two weeks, followed by a 7-day rest period. PET-CT in September 2019 showed the markedly reduction of the local recurrence, and PET-CT in October 2021 showed the complete disappearance of the local recurrence. At 20 months after the discontinuation of S-1, PET-CT showed the complete disappearance of the local recurrence.

Conclusions: Chemotherapy with S-1 can be managed safely and was demonstrated to be effective in treating the local recurrence of GBC recurrence.

KEYWORDS: Gallbladder cancer, S-1, Complete response, PET-CT, Local recurrence.

INTRODUCTION

Surgical resection is the only treatment for biliary tract cancers (BTC) that offers the chance of a radical cure; however, there are many cases of recurrence in the early postoperative period, even in resectable cases. Gallbladder cancer (GBC) is characterized by local invasion, extensive regional lymph node metastasis, vascular encasement, and distant metastasis. Therefore, only 10% of patients present with early-stage disease are candidates for surgery [1]. Although the long-term survival of patients with GBC relies on radical surgery, locoregional or distant recurrence frequently occurs [2,3]. Gemcitabine (GEM) plus cisplatin (CDDP) (GC) combination therapy is the first-line chemotherapy for recurrent or unresectable BTC.

S-1 is a novel orally administered drug composed of a combination of 5-fluorouracil (5-FU) prodrug, tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and oteracil potassium (OXO) in a 1:0.4:1 molar concentration ratio[4]. Based on the results of randomized phase III trials, S-1 has become a key drug in the treatment of advanced gastric cancer in Japan and is the standard option for chemotherapy [5,6]. Furthermore, GEM and S-1 were approved for clinical use in the treatment of BTC by the Ministry of Health, Labour and Welfare in August 2007[7].

We herein report the case of a patient with GBC who developed local recurrence after surgery. Positron emission tomography computed tomography (PET-CT) showed the disappearance of local recurrence with the administration of S-1 therapy as the second-line treatment after surgery.

CASE PRESENTATION

In October 2017, a 69-year-old woman was referred to our hospital with complaints of right hypochondrial pain. Her medical history included Sjögren syndrome and Hashimoto disease. At the patient's baseline physical examination, she had a mass without tenderness in the right hypochondrial region. Laboratory investigations revealed mild anemia, with a normal liver function. Regarding her tumor marker levels, her carcinoembryonic antigen (CEA) level was within the normal range, while her carbohydrate antigen 19-9 (CA19-9) levels were elevated to 535.9 U/ml.

Abdominal ultrasonography revealed wall thickening of the fundus of the gallbladder. Abdominal enhanced computed tomography (CT) showed a 45×38 mm calcified, fluid-filled mass at the base of the gallbladder (Fig. 1a, b). Abdominal magnetic resonance imaging (MRI) showed irregular wall thickening from the gallbladder body to the base, and a diffusion-weighted image showed a markedly high signal intensity (Fig. 1c). Based on these findings, we diagnosed the patient with suspected GBC.

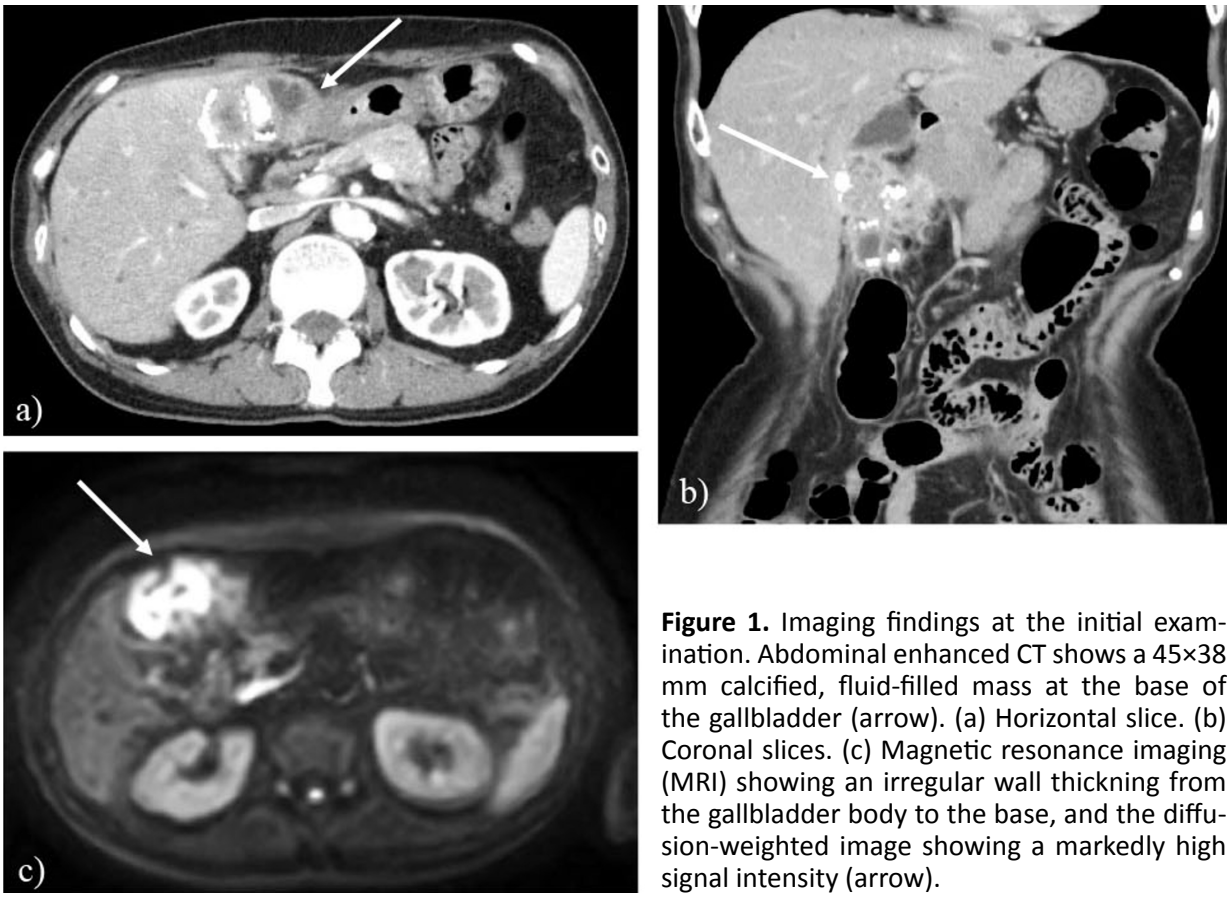

Figure 1. Imaging findings at the initial examination. Abdominal enhanced CT shows a 45×38 mm calcified, fluid-filled mass at the base of the gallbladder (arrow). (a) Horizontal slice. (b) Coronal slices. (c) Magnetic resonance imaging (MRI) showing an irregular wall thickning from the gallbladder body to the base, and the diffusion-weighted image showing a markedly high signal intensity (arrow).

Hepatic floor resection with lymph node dissection, partial resection of the transverse colon, and partial resection of the stomach were performed because of the involvement of the gallbladder base, the gastric wall, and the wall of the transverse colon. A histopathological examination revealed a nodular infiltrating type of 70×65 mm in size. The diagnosis was moderately differentiated tubular adenocarcinoma, pT3 (liver), N0, M0, pStage IIIA according to the Union for International Cancer Control TMN classification of malignant tumors (8th edition)[8].

The patient was discharged from the hospital on the 9th day after surgery with a good postoperative course. During outpatient follow-up, local recurrence was observed on abdominal enhanced CT (Fig. 2a, b) and PET-CT in March 2018 (Fig. 2c, d). In GC therapy, each cycle consisted of CDDP (25 mg/m^2)

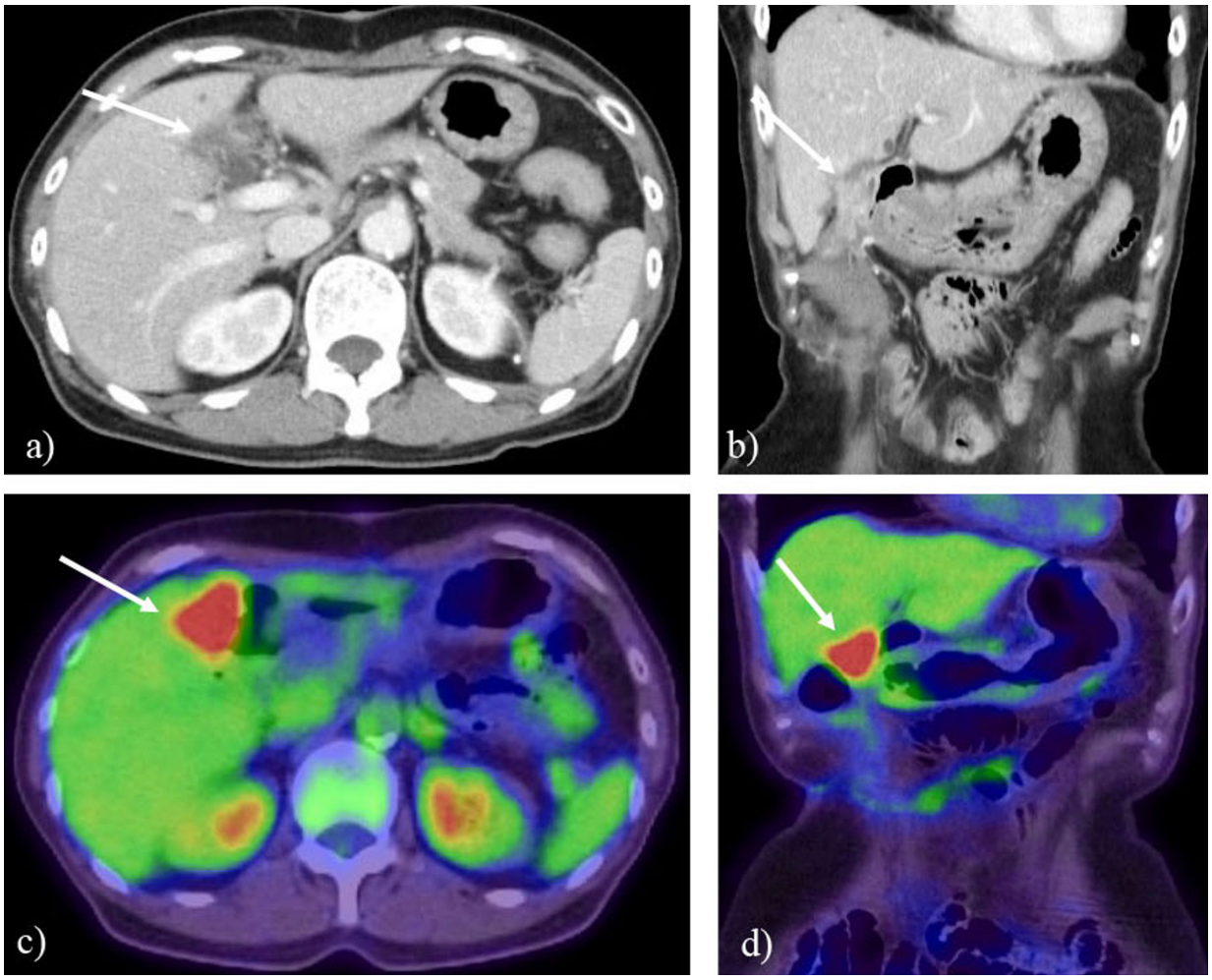

Figure 2. Imaging findings of local recurrence. Local recurrence was observed by abdominal enhanced CT (arrow). (a) Horizontal slice. (b) Coronal slices. Local recurrence was observed by PET-CT (arrow). (c) Horizontal slice. (d) Coronal slices.

followed by GEM (1,000 mg/m^2), administered on days 1 and 8 every 3 weeks. GC therapy was initiated, and nine courses were administered; PET-CT in March 2018 showed increased local recurrence. The CEA level was elevated to 10.6 ng/ml. Based on these findings we considered that the GC therapy was ineffective. With informed consent from the patient, we initiated second-line chemotherapy with S-1 (60 mg/day) administered for two weeks, followed by a 7-day rest period as a cycle. In April 2019, abdominal enhanced CT showed no evidence of local tumor recurrence (Fig. 3). In September 2019, PET-CT showed markedly reduced local recurrence (Fig. 4a, b). PET-CT in October 2021 showed the complete disappearance of the local recurrence (Fig. 4c, d). The CEA levels were also within the normal range. At 20 months after the discontinuation of S-1, PET-CT showed the complete disappearance of the local recurrence. The patient's only adverse events, according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0[9] were only grade 2 watering eyes, and increased creatinine.

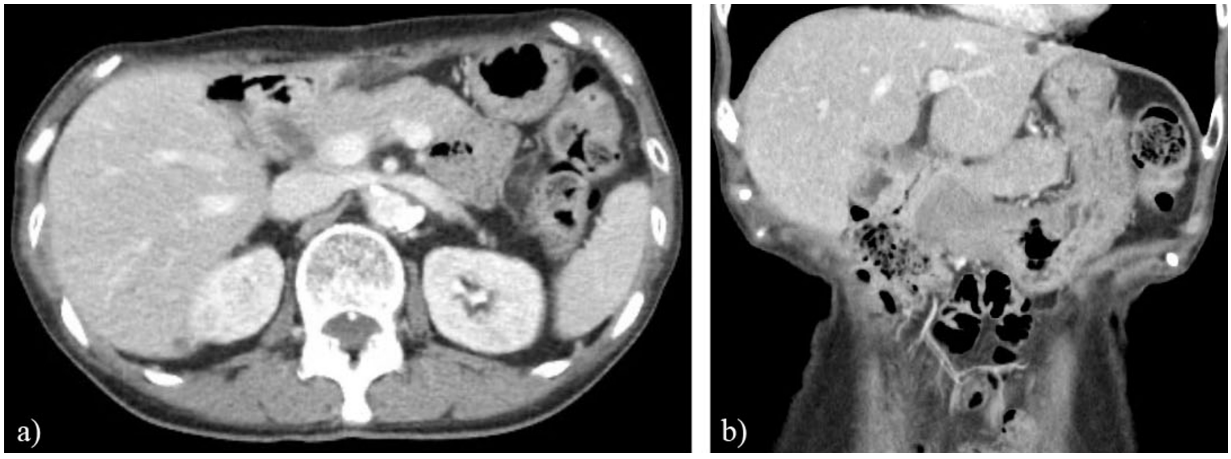

Figure 3. Abdominal contrast CT findings in April 2019. There was no evidence of local tumor recurrence on abdominal enhanced CT. (a) Horizontal slice. (b) Coronal slices.

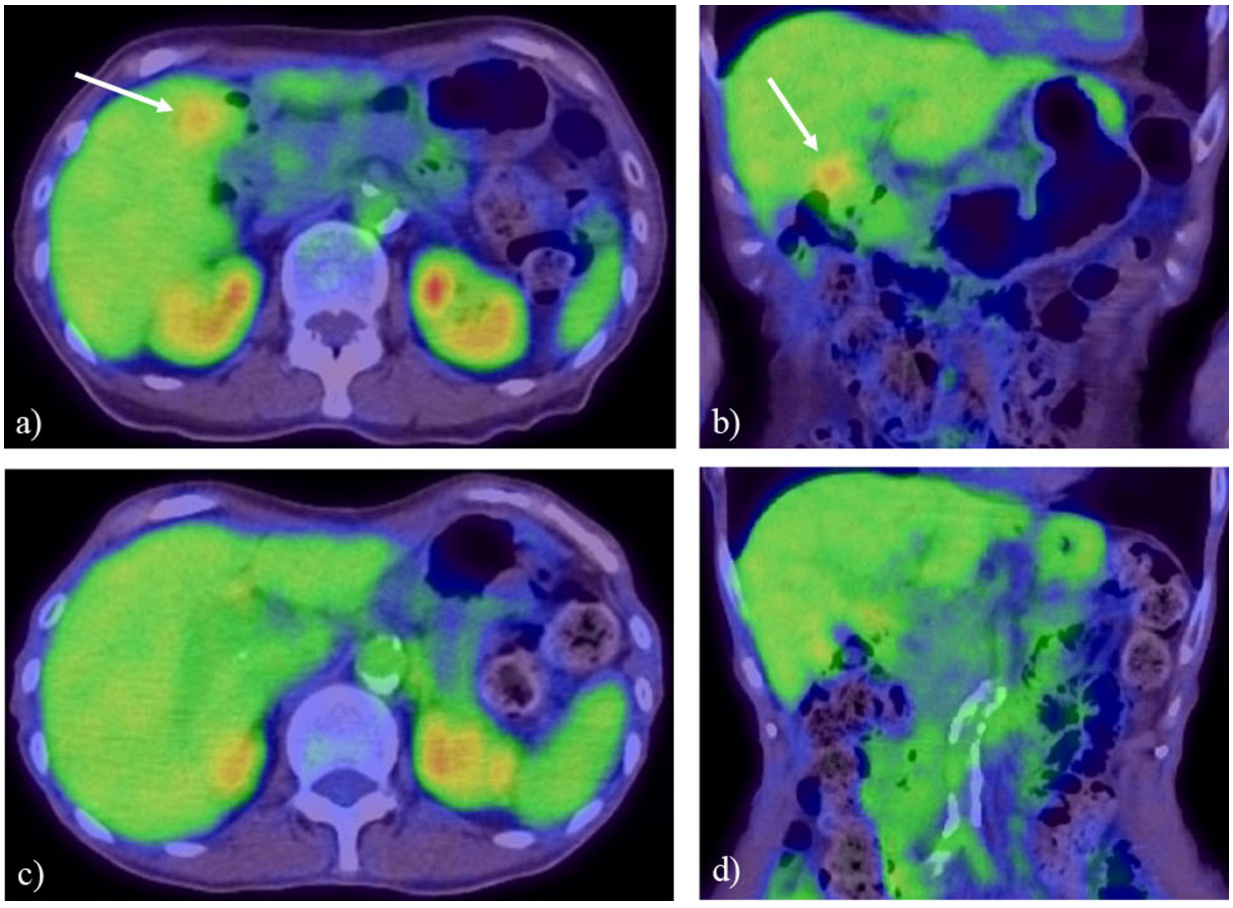

Figure 4. PET-CT findings during S-1 administration. PET-CT in September 2019 showed the markedly reduction of local recurrence (arrow). (a) Horizontal slice. (b) Coronal slices. The locally recurrent tumor had completely disappeared on PET-CT in October 2021. (c) Horizontal slice. (d) Coronal slices.

DISCUSSION

Surgical resection is the treatment for GBC that is most likely to achieve a cure of GBC; however, the early detection of GBC is difficult due to its asymptomatic nature in the early stages [10]. BTC, including GBC, has a poor prognosis with an estimated 5-year survival rate of < 20%. For patients with advanced-stage or unresectable BTC, the first-line systemic chemotherapy is GC therapy. However, this first-line standard of care has limited effectiveness, with a median overall survival time of <1 year [11]. We performed first-line GC therapy for postoperative local recurrence of GBC. We considered that the first-line GC therapy was ineffective after 8 months of treatment.

The novel antitumor drug S-1 contains a prodrug of 5-FU and was developed based on the biochemical effects of CDHP, a dihydropyrimidine dehydrogenase (DPD) inhibitor, and OXO, an orotate phosphoribosyltransferase (OPRT) inhibitor, in the small intestine. The principal role of these modulators is to inhibit the degradation of 5-FU-induced gastrointestinal toxicity. Thymidylate synthase (TS), which inhibits DNA synthesis, is a major target of 5-FU. High TS activity in cancer tissue is considered to reduce the efficacy of 5-FU, and it is likely that the DPD mRNA level is also a significant predictor of the response to 5-FU. Low TS and DPD expression levels are associated with poor outcomes in colorectal cancer patients treated with surgery alone, whereas low expression levels are associated with improved outcomes in patients treated with 5-FU chemotherapy[12].

Inoue et al[13] reported the first study assessing the efficacy and safety of S-1 in patients with unresectable and recurrent BTC for whom GC therapy the current standard first-line therapy failed. Suzuki et al[14] reported that the median progression-free survival (PFS) and overall survival (OS) were 2.5 and 6.8 months, respectively, and Kobayashi et al[15] reported that the median PFS and OS were 2.3 and 6.0 months, respectively. S-1 has a certain degree of efficacy in patients who have become refractory to GEM monotherapy and GC therapy. Sasaki et al[16] showed better results than other studies: the median PFS and OS were 5.4 and 13.5 months, respectively.

Two similar case reports were found after doing a literature search. In one study, a 60-year-old woman was referred with complaints of jaundice. Abdominal CT showed the presence of advanced GBC, which had invaded the liver masa well as regional lymph node metastasis and perineural invasion of the common hepatic and celiac arteries. The tumor was concluded to be inoperable due to the presence of perineural invasion of the common hepatic and celiac arteries. S-1 was initiated at a dose of 100 mg twice daily for four weeks, followed by a 14-day rest period, for a total of 25 cycles. CT scan demonstrated a clear reduction in size in the regions of the liver that were invaded by the GBC, as well as those affected by lymph nide metastasis and perineural invasion. The patient underwent successful surgical curative resection [17]. In another study, an 86-year-old woman underwent surgical resection for GBC. At seven months after surgery, multiple live and lymph nide metastases were observed on abdominal CT scan. With informed consent from the patient, chemotherapy with S-1 was initiated every other day. At seven months after administration of S-1, multiple liver and lymph node metastases disappeared on imaging examinations[18].

There was one case report of tumor disappearance by PETCT regarding chemotherapy for GBC. A 67-year-old man with metastatic gallbladder cancer involving the liver and abdominal lymph nodes was treated with gemcitabine (1000 mg/m^2) on day 1 and 8 every 21 days as well as daily erlotinib (100 mg). After four cycles of therapy, the CA 19-9 normalized and a PETCT showed a complete remission; this response was maintained by the end of 12 cycles of therapy. Gemcitabine was then discontinued and single agent erlotinib was continued as maintenance therapy. The disease remains in good control 18 months after initiation of therapy, including 6 months on maintenance erlotinib. The only grade 3 toxicity was a typical EGFR-related skin rash[19].

Accordingly, we selected S-1 monotherapy as the second-line treatment. In our case, we performed CT scans every four months during chemotherapy with S-1. The patient's tumor marker levels normalized in September 2021, and the locally recurrent tumor completely disappeared on PET-CT in October 2021. At 20 months after the discontinuation of S-1, there is still no sign of the tumor on PET-CT. These results suggest that medical treatment with S-1 may be effective in treating local recurrence after GBC surgery. The patient experienced grade 2 adverse events of watering eyes, and increased creatinine.

Tumor Disappearance on PETCT after S-1 Treatment for Postoperative Local Recurrence of GBC" is the first case of this title that has not been published in the literature.

CONCLUSIONS

We reported the case of a patient with GBC with local recurrence after surgery. The disappearance of a recurret tumor on PET-CT was observed with S-1. Chemotherapy with S-1 can be managed safely and its efficacy in the treatment of local recurrence of GBC has been demonstrated.

Conflicts of interest:

All authors declare that there are no conflicts of interest.

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TU reported the case and drafted the manuscript. TU and IE performed the surgery, and YN helped draft the manuscript. OY, HA, and MK participated in revising the manuscript critically. All authors declare that they contributed to this article that they read and approved the final manuscript.

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All data generated or analyzed during this study are included in this published article.

Consent for publication:

Consent to publish was obtained from the patient.

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