Case Report

Response to anti-EGFR therapy in chemo-refractory right-sided RAS wild-type metastatic colorectal cancer: a case report and literature review

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Background: Anti-epidermal growth factor receptor (EGFR) therapies are important targeted agents in the treatment of metastatic colorectal cancer (CRC). However, clinical benefit is limited to patients with left-sided primary tumors and RAS wild-type (WT) disease. In right-sided chemo-refractory settings, response to anti-EGFR therapy has not been reported to date.

Case Description: We present a case of a 70-year-old man with metachronous metastatic ascending colon adenocarcinoma who experienced an exceptional response to FOLFIRI (fluorouracil, leucovorin, and irinotecan) plus panitumumab after failing multiple lines of therapy. He was initially diagnosed with stage IIIB (pT4aN1M0) disease and underwent hemicolectomy followed by adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin). Nine months after completion of adjuvant therapy, disease recurred in the liver, peritoneum, and mesenteric lymph nodes. Subsequent treatments included FOLFIRI plus bevacizumab and FOLFOX with eventual progression. Tumor genomic profiling revealed RAS/RAF WT disease, and in the absence of anti-EGFR therapy resistance mutations, the patient was offered treatment with FOLFIRI plus panitumumab. He achieved immediate palliation of his abdominal pain after one cycle, followed by normalization of his tumor markers and significant tumor regression of his hepatic, peritoneal, lung, and distant lymph node metastases within four cycles.

Conclusions: Treatment options for right-sided RAS-WT metastatic CRC are limited, particularly after progression on standard chemotherapies. While anti-EGFR antibodies have demonstrated detrimental survival impact in the first-line setting for right-sided CRC, their performance in later lines is less well-characterized. This case challenges the notion of right-sided disease as uniformly resistant to EGFR inhibition and highlights the need for additional biomarker studies to identify the subset of right-sided CRC that may benefit from EGFR targeted strategies. Emerging evidence suggests that more stringent genomic criteria for EGFR resistance, beyond RAS mutation status alone, may refine patient selection for benefit from anti-EGFR therapies.

Keywords: Colorectal cancer (CRC); right-sided tumor; RAS wildtype; epidermal growth factor receptor therapy (EGFR therapy); case report

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Introduction

Anti-epidermal growth factor receptor (EGFR) therapies, such as cetuximab and panitumumab, are important targeted agents in the colorectal cancer (CRC) treatment landscape. These monoclonal antibodies competitively bind to EGFR and disrupt downstream signaling cascades vital for cell proliferation and survival. However, only a subset of patients derive benefit. RAS mutation status and primary tumor sidedness have emerged as key predictive biomarkers of anti-EGFR efficacy. Whereas the addition of cetuximab or panitumumab to first-line chemotherapy confers no benefit in RAS mutated tumors, EGFR inhibition in RAS wild-type (WT) disease enhances response rates (RRs) by roughly 10–20% and extends median overall survival (OS) by 3- to 4-month compared to chemotherapy alone (1-3).

Beyond RAS status, primary tumor location has also been strongly correlated with anti-EGFR efficacy in post-hoc pooled analyses (4). In phase III CRYSTAL and PRIME trials, the addition of cetuximab or panitumumab to front-line doublet chemotherapy was associated with prolonged median OS (28.7 *vs.* 21.7 months; 30.3 *vs.* 23.6 months, respectively) and augmented RR (72.5% *vs.* 40.6%; 67.9% *vs.* 52.6%, respectively) in left-sided subgroups only. No benefit was observed in right-sided disease. The CALGB/SWOG 80405 and FIRE-3 trials comparing cetuximab- *vs.* bevacizumab-containing regimens also demonstrated an OS advantage (median 39.3 *vs.* 32.6 months; 38.2 *vs.* 28.2 months, respectively) in favor of anti-EGFR therapy among patients with left-sided primary tumors, an observation that was prospectively confirmed in the PARADIGM trial (5). Conversely, in right-sided disease, cetuximab use was associated with shorter median OS (13.6 *vs.* 29.2 months; 18.5 *vs.* 23 months, respectively), suggesting a possible detrimental effect of front-line anti-EGFR therapies in this subgroup (6,7). Although the exact biological basis behind this right-versus-left phenomenon is not fully understood, tumor location likely reflects distinct molecular and clinicopathologic differences between proximal and distal CRC (8-10).

Based on these large-scale retrospective analyses, anti-EGFR antibodies are aptly excluded from the first-line treatment of metastatic right-sided CRC. Their role in second-line and beyond settings, however, remains poorly defined. Three randomized phase III trials—EPIC, 20050181, and PICCOLO—have noted improvements in RR (16.4% *vs.* 4.2%; 36% *vs.* 10%; and 34% *vs.* 12%, respectively) and median progression-free survival (PFS) (4 *vs.* 2.6 months; 6.7 *vs.* 4.9 months; and not reported, respectively) when anti-EGFR is added to second-line chemotherapy. However, these benefits were not upheld in subgroup analyses of right-sided tumors (11). At best, the 20050181 trial reported numerically, but statistically insignificant, improved median OS (10.3 *vs.* 8.1 months), PFS (4.8 *vs.* 2.4 months), and RR (13.3% *vs.* 2.6%) with the addition of panitumumab to second-line FOLFIRI (fluorouracil, leucovorin, and irinotecan) in the right-sided cohort (4). Whereas left-sided tumors gain PFS and RR advantage from the addition of anti-EGFR therapy to second-line chemotherapy, right-sided tumors do not.

Data on anti-EGFR efficacy in right-sided CRC in third-line and beyond settings are even less robust. In this context, three randomized phase III trials—20020408, NCIC CTG CO.17, and 20100007—compared the addition of single-agent cetuximab or panitumumab to best supportive care (BSC) in chemo-refractory or chemo-ineligible metastatic CRC. In RAS-WT populations, the CO.17 and 20100007 trials showed OS advantage (median 9.5 *vs.* 4.8 months; 10 *vs.* 6.9 months, respectively) with anti-EGFR therapy (12-14). The third trial—20020408—demonstrated PFS benefit by a small but statistically significant margin (2.83 *vs.* 1.68 months); any potential signal for improved OS was likely diluted due to cross-over design (15,16). Of these three studies, the CO.17 and 20020408 trials were later re-visited to assess the impact of tumor sidedness on anti-EGFR treatment efficacy. Both analyses confirmed that

Highlight box

Key findings

- Anti-epidermal growth factor receptor (EGFR) antibody in combination with chemotherapy demonstrated clinical benefit in chemo-refractory right-sided RAS wild-type (WT) metastatic colorectal cancer (CRC).

What is known and what is new?

- Anti-EGFR therapies have historically been excluded from the treatment paradigm of right-sided metastatic CRC due to limited efficacy and potential detrimental survival impact.
- In the absence of effective alternative therapies, anti-EGFR antibodies should be considered for patients with refractory right-sided RAS-WT CRC lacking known anti-EGFR resistance alterations.

What is the implication, and what should change now?

- There may be an underrecognized subset of patients with right-sided CRC who might benefit from anti-EGFR therapy. Additional biomarker studies are needed to identify this population.

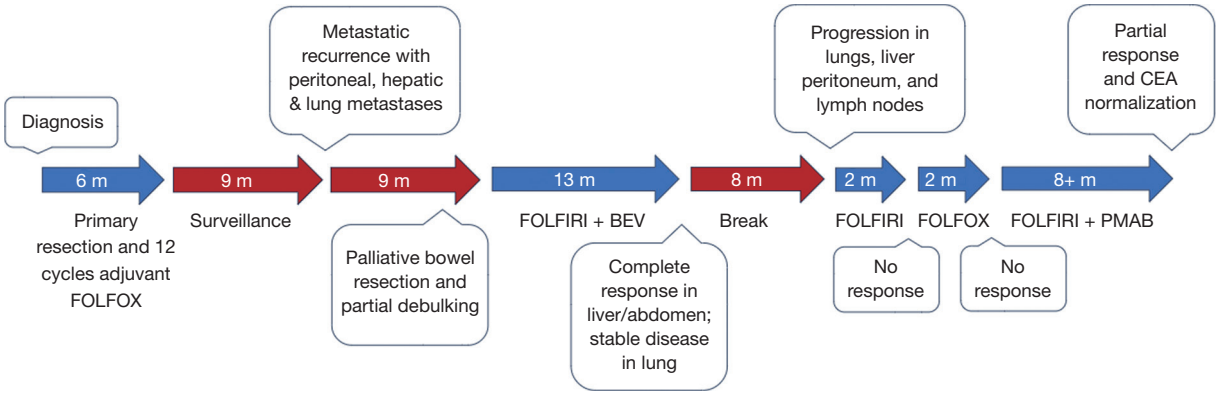

Figure 1 Treatment timeline, with duration displayed in months. Blue arrows indicate periods of active systemic treatment. Red arrows indicate periods of surveillance or monitoring off treatment per patient preference. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFIRI, fluorouracil, leucovorin, and irinotecan; BEV, bevacizumab; PMAB, panitumumab; CEA, carcinoembryonic antigen.

left-sided primary tumor location is strongly associated with anti-EGFR treatment benefit, resulting in improved median PFS (5.4 *vs.* 1.8 months; 5.5 *vs.* 1.6 months, respectively) and OS (10.1 *vs.* 4.8 months in the CO.17 study only) (17,18). No substantial advantage was reported in right-sided tumors, although cetuximab elicited a modest numeric, but statistically insignificant, improvement in median OS (6.2 *vs.* 3.5 months) in the CO.17 RAS-WT right-sided cohort (n=56) (17). In the 20020408 RAS-WT right-sided cohort (n=30), panitumumab added to BSC did not improve median OS (3.1 *vs.* 4.6 months) or PFS (1.9 *vs.* 1.7 months) (18). In both studies of chemo-refractory disease, RRs to anti-EGFR monotherapy differed drastically by primary tumor location (0% *vs.* 23% and 0% *vs.* 24% in right- versus left-sided tumors in CO.17 and 20020408, respectively) (18,19). Similarly, a retrospective analysis of third-line anti-EGFR monotherapy or cetuximab-irinotecan (in irinotecan-refractory disease) reported zero responses (out of 14) in right-sided tumors compared to 41% RR among left-sided CRC (20).

Taken together, these data portray anti-EGFR monotherapy in refractory right-sided CRCs in a discouraging light. Combination strategies of anti-EGFR plus chemotherapy, however, may fare better and have been prospectively studied in the BOND and ICECREAM trials (21,22). Even in irinotecan-refractory disease, the addition of irinotecan to anti-EGFR therapy more than doubled RR (22.9% *vs.* 10.8%; 38% *vs.* 10%, respectively) and improved 6-month PFS rates by 3-fold (30% *vs.* 8%; 41% *vs.* 14%, respectively). However, it remains to be seen whether this benefit applies to right-sided CRC, as the BOND trial was not stratified by tumor location and the ICECREAM study recruited predominantly left-sided tumors. Based on our review of the literature, there have been no robust clinical responses to EGFR targeted therapy described in chemo-refractory right-sided RAS-WT colon cancer to date. Here, we report a case of RAS-WT metastatic cecal adenocarcinoma with durable objective response to FOLFIRI + panitumumab following FOLFIRI + bevacizumab and FOLFOX (fluorouracil, leucovorin, and oxaliplatin) progression. This case challenges the assumption that right-sided disease is uniformly resistant to EGFR inhibition and highlights the need for additional biomarker studies to identify the subset of right-sided CRC that may benefit from EGFR targeted therapies. We present this case in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-458/rc).

Case presentation

This is a 70-year-old male with a history of low-risk prostate cancer on active surveillance, who was initially diagnosed with stage IIIB (pT4aN1M0) ascending colon adenocarcinoma in November 2018. The treatment timeline is illustrated in *Figure 1*. He underwent definitive right hemicolectomy followed by 12 cycles of adjuvant FOLFOX chemotherapy, completed in July 2019. Surveillance computed tomography (CT) imaging in April 2020 showed disease recurrence with multiple positron emission tomography (PET)-confirmed peritoneal soft tissue densities and two hepatic metastases. Treatment

was delayed due to the patient's hesitancy to proceed with systemic therapy. In August 2020, he began experiencing progressive abdominal pain and obstipation. Magnetic resonance imaging (MRI) scans later revealed evidence of severe intestinal dilatation, at which point he transferred to our care. Based on his imaging findings and highly symptomatic condition, he was taken to surgery in November 2020 for palliative bowel resection and partial peritoneal tumor debulking at the focal level of obstruction. The resected specimens provided histopathologic confirmation of metastatic disease, and genomic analysis by Clinical Laboratory Improvement Amendments (CLIA) certified next generation sequencing (NGS) revealed microsatellite stable, RAS/RAF-WT, *TP53* V122fs mutated (34%), and *KDM6A* V326fs mutated (11%) disease, which was consistent with the molecular profile of his primary tumor specimen. Other significant alterations included structural inversion of *CTNNB1*, *SOX9* H380fs (31%), and multiple chromosomal imbalances including loss of heterozygosity (LOH) of chromosome 18 and gain of chromosome or chromosome arms 8q (partial), 13q (partial) and 20. Germline testing did not reveal any known pathogenic variants.

In January 2021, he began systemic chemotherapy with FOLFIRI + bevacizumab for residual metastatic disease in the liver, mesenteric lymph nodes, and low-volume carcinomatosis. He achieved a complete response of his mesenteric/retroperitoneal mass and two hepatic lesions, along with disease stabilization in his lungs. After a total of 26 cycles completed in March 2022, our patient desired a complete treatment break. From there, he had sporadic follow-up, but ultimately re-presented in November 2022 with worsened bloating and abdominal pain. Imaging showed significant progression of disease in the lungs, as well as numerous new hepatic, peritoneal, and distant lymph node metastases. He resumed FOLFIRI in November 2022. Bevacizumab was withheld due to poorly controlled hypertension and non-adherence to anti-hypertensive medications. He received four cycles until re-staging scans in January 2023 demonstrated worsening disease in the liver and lungs. He was rechallenged with FOLFOX beginning in February 2023, but only received four cycles before overt radiographic progression. In the absence of any molecular biomarkers associated with anti-EGFR resistance, we offered to treat him with combination cytotoxic chemotherapy plus EGFR-targeted antibody. He began FOLFIRI + panitumumab in April 2023 and derived immediate clinical benefit with palliation of his abdominal pain after one cycle, followed by normalization of his serum carcinoembryonic antigen (CEA) level after four cycles (*Figure 2A*). CT imaging showed remarkable early tumor shrinkage after four cycles, with sustained and global disease regression after 16 cycles (*Figure 2B-2D*). The patient had an overall positive treatment experience with rapid resolution of his nausea and abdominal pain, gradual 10-pound weight gain, and a return to his baseline energy level. Although he developed a mild acneiform rash over the scalp and face related to panitumumab, this was not bothersome to him and improved with adherence to doxycycline.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

To our knowledge, this is the first documented response to anti-EGFR therapy in chemo-refractory right-sided RAS-WT colon cancer. Several factors could have contributed to his excellent response. First, his tumor lacked any genomic alterations associated with inherent anti-EGFR resistance. Beyond *KRAS* mutations, other genomic alterations—such as *HRAS*, *NRAS*, *BRAF*, and certain *PIK3CA* mutations, as well as *HER2* or *MET* amplifications—have also demonstrated poor sensitivity to EGFR-targeted treatments (23,24), none of which were identified in our patient's tumor sample. Second, despite the traditionally worse prognosis and shorter OS of right-sided CRCs (25-27), our patient exhibited more favorable disease biology than typical of this subgroup. His disease was managed with combination chemotherapy and intermittent treatment breaks for 3 years before becoming triple chemo-refractory. Lastly, while tumor sidedness is strongly prognostic at the time of diagnosis (27-29), this distinction may have diminishing relevance in later line settings (17), possibly due to the negative selection of highly aggressive disease phenotypes over time. Our search for alternative explanations to justify his excellent treatment response did not yield significant findings. High *EGFR* gene copy number, which has been linked to higher RR and prolonged PFS (30), was not detected in our patient's tumor. EGFR expression by

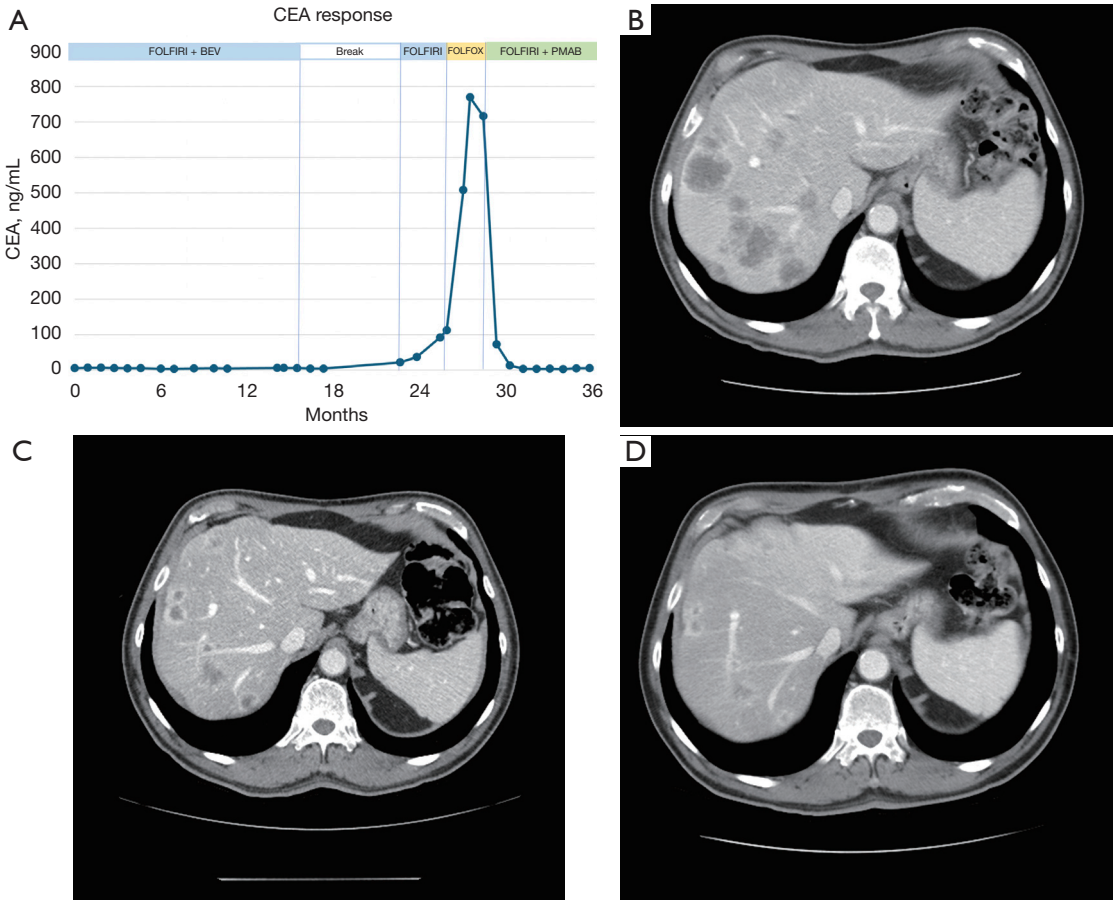

Figure 2 Response to FOLFIRI plus panitumumab. (A) Treatment timeline and CEA serum level trend from time of initiation of systemic therapy for metastatic disease. (B) Representative CT image of baseline liver disease burden prior to initiation of anti-EGFR therapy. Comparative CT image showing hepatic disease regression after (C) 4 cycles and (D) 16 cycles of FOLFIRI plus panitumumab, respectively. CEA, carcinoembryonic antigen; FOLFIRI, fluorouracil, leucovorin, and irinotecan; BEV, bevacizumab; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; PMAB, panitumumab; CT, computed tomography; EGFR, epidermal growth factor receptor.

immunohistochemistry is not predictive of response to EGFR-targeted therapies, and thus was not assessed in this case. Finally, the possibility of a missed synchronous left-sided tumor is unlikely, as the patient's initial colonoscopy in November 2018 and surveillance colonoscopy in January 2020 did not show any evidence of intraluminal masses in the left colon. Moreover, genomic profiling of his metastatic site was identical to that of his original cecal mass.

Although the precise reasoning for our patient's remarkable treatment response remains unknown, this case more importantly highlights the gaps in evidence surrounding anti-EGFR therapies in refractory and right-sided disease settings. While there is a clear consensus regarding the lack of benefit of first-line anti-EGFR therapy in right-sided CRC, evidence to guide its use in later lines is limited to data extrapolated from retrospective analyses, which lack randomization, prospective design, and adequate control arms or sample size. Acknowledging the insufficient data, the National Comprehensive Cancer Network (NCCN) panel recommends that panitumumab or cetuximab be considered in subsequent lines of therapy irrespective of tumor sidedness. Given the incremental gains offered by current standard third-line treatments (with RR of 1–6% and median PFS ranging from 2 to 6 months), the potential of anti-EGFR combination therapies should not be prematurely discounted. Retrospective studies have reported double-digit RR (11%, or 1 of 9 patients, in one study and 14.3%, or 6 of 42 patients, in another)

with third-line anti-EGFR plus concurrent chemotherapy in right-sided tumor subgroups (31,32). However, it is unclear whether these were observed in truly triple chemo-refractory settings, as in our patient's case. More than 20% of patients in the first study did not have prior exposure to oxaliplatin or irinotecan, and 40% of patients in the second study had metachronous metastases where adjuvant therapy may or may not have constituted a prior line of therapy. However, as illustrated by our patient's prolonged treatment response, there may exist an underrecognized subset of right-sided tumors that stands to benefit from EGFR-targeting strategies.

Efforts to accurately predict responses to anti-EGFR treatment are still underway. Amphiregulin (AREG) and epiregulin (EREG) are two endogenous EGFR ligands that have been associated with anti-EGFR efficacy in RAS-WT CRC (33). The PICCOLO trial identified a subset of right-sided tumors with high AREG/EREG expression that responded favorably to EGFR inhibition (11,34), suggesting that these biomarkers could potentially overcome baseline differences between right- and left-sided CRC. This is currently being evaluated prospectively in the phase IV ARIEL trial of patients with high AREG/EREG-expressing, untreated right-sided RAS-WT metastatic CRC, randomized to chemotherapy with or without an anti-EGFR agent (35). Other expanded biomarker panels have also been shown to refine responses to anti-EGFR therapy. In an exploratory analysis of CALGB/SWOG 80405, *HER2* gene expression was identified as a potential prognostic and predictive biomarker of survival benefit from first-line cetuximab over bevacizumab (36). In a prespecified post hoc analysis of another front-line study—the PARADIGM trial—patients with right-sided tumors lacking any circulating tumor DNA (ctDNA)-detected EGFR resistance alterations—such as *KRAS/NRAS*, *PTEN*, *EGFR*, *HER2*, *MET*, *ALK*, *RET*, and *NTRK1*—experienced a longer median OS (38.9 *vs.* 30.9 months) when treated with panitumumab than with bevacizumab (37), suggesting that ctDNA biomarkers may better predict response to anti-EGFR therapy than tumor sidedness alone. ctDNA has also been applied to anti-EGFR rechallenge strategies, where retained RAS/BRAF-wildtype status at the time of rechallenge has been associated with antitumor activity in refractory metastatic disease (38). While these findings have improved our understanding of anti-EGFR treatment efficacy, this case illustrates the possibility for clinical benefit from anti-EGFR therapy in chemo-refractory right-sided RAS-WT metastatic CRC, underscoring the need for better predictive biomarkers of response.

Conclusions

Here we present a patient with chemo-refractory right-sided RAS-WT metastatic CRC who had an exceptional response to anti-EGFR therapy. This case challenges the notion that all right-sided disease is resistant to EGFR inhibition and highlights the need for additional biomarker studies to identify the subset of right-sided CRC that may benefit from EGFR targeted strategies. Emerging evidence suggests that more stringent genomic criteria for EGFR resistance, beyond RAS mutation status alone, may refine patient selection for benefit from anti-EGFR therapies.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-458/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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