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LONG-TERM PROGRESSION-FREE SURVIVAL FOLLOWING MULTIMODAL THERAPY FOR MUCINOUS ADENOCARCINOMA OF THE APPENDIX: A CASE REPORT

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DUGOTRAJNO PREŽIVLJAVANJE BEZ PROGRESIJE BOLESTI KOD PACIJENTKINJE SA MUCINOZNIM ADENOKARCINOMOM SLEPOG CREVA I PERITONEALNOM KARCINOMATOZOM – PRIKAZ SLUČAJA

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ABSTRACT

Introduction: Primary adenocarcinoma of the appendix is a rare and heterogeneous malignancy, most commonly presenting as mucinous adenocarcinoma. Due to its nonspecific clinical manifestations, the diagnosis is often established at an advanced stage, frequently with already present peritoneal dissemination. Standard treatment for advanced mucinous appendiceal carcinoma involves cytoreductive surgery with HIPEC followed by systemic chemotherapy, or initial systemic therapy for downstaging, followed by repeat CRS and HIPEC. In cases where radical surgery is not feasible, the average survival is less than one year.

Case report: We report a case of a 72-year-old woman with no relevant family history, who presented with acute right lower abdominal pain and distension. Imaging revealed multiple cystic peritoneal implants, ascites, and small bowel obstruction. Palliative emergency surgery demonstrated an appendiceal mass invading the right ovary, with widespread peritoneal mucinous deposits. Histopathological analysis confirmed mucinous adenocarcinoma of the appendix with peritoneal carcinomatosis.

Postoperatively, the patient received 12 cycles of bevacizumab plus FOLFOX chemotherapy, achieving marked radiologic and biochemical improvement. Maintenance therapy with bevacizumab plus 5-FU/LV led to sustained disease stabilization. After 32 cycles, the patient developed an entero-vaginal fistula, which was surgically managed due to poor quality of life. Intraoperatively, the decision was made for cytoreductive surgery and fistulectomy. Postoperative imaging showed no evidence of disease. The patient remains progression-free for nearly three years, and disease-free for one year.

Conclusion: This case highlights the potential for long-term survival in initially inoperable patients with advanced mucinous appendiceal adenocarcinoma and peritoneal carcinomatosis when treated with combined cytoreductive surgery and bevacizumab plus chemotherapy. Multimodal and individualized treatment strategies may significantly improve outcomes in this rare malignancy.

Keywords: mucinous adenocarcinoma, bevacizumab, peritoneal carcinomatosis, multimodal treatment

SAŽETAK

Uvod: Primarni adenokarcinom slepog creva predstavlja retku i heterogenu malignu bolest, pri čemu je mucinozni adenokarcinom najčešći histološki podtip. Zbog nespecifičnih kliničkih manifestacija, dijagnoza se često postavlja u odmaklom stadijumu i sa već prisutnom peritonealnom diseminacijom. Standardno lečenje uznapredovalog mucinoznog karcinoma apendiksa podrazumeva citoreduktivnu hirurgiju sa HIPEC procedurom uz sistemsku hemioterapiju, ili primenu sistemske terapije radi downstaginga, a zatim ponovljenu CRS i HIPEC proceduru. U situacijama kada nije moguća radikalna operacija, prosečno preživljavanje je kraće od jedne godine.

Prikaz slučaja: Prikazujemo slučaj 72-godišnje pacijentkinje, koja se javila zbog naglo nastalog bola u desnom donjem kvadrantu abdomena i abdominalne distenzije. Radiološkim ispitivanjem otkriveni su brojni cistični peritonealni implanti, ascites i distenzija tankog creva. Sprovedeno je hitno operativno lečenje kada je verifikovana tumorska masa apendiksa sa invazijom desnog jajnika i brojnim mucinoznim depozitima u peritonealnoj duplji. Histopatološki nalaz potvrdio je mucinozni adenokarcinom apendiksa sa peritonealnom karcinomatozom.

Postoperativno je primenjeno 12 ciklusa hemioterapije po režimu bevacizumab + FOLFOX, nakon čega je postignuto značajno kliničko poboljšanje i radiološka regresija uz normalizaciju tumorskih markera. Terapija održavanja bevacizumab + 5-FU/LV dovela je do stabilizacije prethodno postignutog odgovora. Nakon 32 ciklusa lečenja pacijentkinja je razvila enterovaginalnu fistulu, koja je hirurški rešena citoreduktivnom operacijom i fistulektomijom. Postoperativna radiološka ispitivanja nisu pokazala prisustvo rezidualne bolesti. Pacijentkinja je bez progresije bolesti gotovo tri godine, a bez znakova relapsa godinu dana.

Zaključak: Ovaj slučaj ukazuje na mogućnost dugotrajnog preživljavanja kod pacijenata sa inicijalno inoperabilnim mucinoznim adenokarcinomom slepog creva i peritonealnom karcinomatozom uz kombinovano lečenje citoreduktivnom hirurgijom i bevacizumabom uz hemioterapiju. Multimodalni i individualizovani terapijski pristup može značajno poboljšati ishod kod ove retke maligne bolesti.

Ključne reči: mucinozni adenokarcinom, bevacizumab, peritonealna karcinomatoza, multimodalno lečenje

INTRODUCTION

Primary adenocarcinoma of the appendix (AA) is a rare and heterogeneous disease, with mucinous adenocarcinoma being the most common histological subtype (1,2). Mucinous appendiceal adenocarcinomas frequently harbor activating KRAS and GNAS mutations, which drive mucin hypersecretion and distinct oncogenic signaling through MAPK and cAMP pathways, distinguishing them from conventional colorectal adenocarcinomas. Due to its nonspecific clinical manifestations, the diagnosis is often established at an advanced stage, frequently with peritoneal dissemination already present.

Standard treatment for advanced mucinous appendiceal carcinoma involves cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) followed by systemic chemotherapy. In cases where radical surgery is not feasible, the average survival is less than one year (3).

Patients with inoperable AA are treated with systemic chemotherapy approved for metastatic colorectal cancer (CRC), although AA differs from CRC in several biological and clinical aspects (4,5).

CASE REPORT

A 72-year-old woman with no family history of colorectal cancer or inflammatory bowel disease presented to our surgical clinic with sudden onset of right lower abdominal pain and abdominal distension. Her medical history included heart arrhythmia treated with verapamil and an oral anticoagulant. She was a smoker and denied alcohol abuse.

On presentation, her vital signs were normal. Physical examination revealed a palpable mass in the right iliac fossa. Abdominal computed tomography (CT) demonstrated multiple cystic peritoneal implants, ascites, and small bowel obstruction.

Given the findings and acute symptoms, emergency exploratory laparotomy was performed the same day. Intraoperatively, an appendiceal mass infiltrating the entire wall of the appendix and invading the right ovary was observed, along with extensive nodular peritoneal implants with pseudomyxoma involving the peritoneal cavity, greater omentum, small bowel mesentery, and both hepatic and splenic regions. Ileocecal resection with primary anastomosis and multiple tumor and peritoneal biopsies were performed.

Histopathology confirmed mucinous adenocarcinoma of the appendix with peritoneal carcinomatosis. Postoperative MRI described an irregular cystic tumor in the right iliac fossa (59 × 57 × 49 mm) and multiple cystic peritoneal implants (largest 81 × 59 × 37 mm) with dense ascitic fluid (Figure 1). Thoracic CT showed no metastatic lesions. Laboratory tests revealed elevated tumor markers: CEA 7.3 ng/mL, CA-125 28.7 U/mL, and CA 19-9 89.9 U/mL.

The patient was subsequently treated with bevacizumab plus FOLFOX regimen for 12 cycles. Follow-up MRI demonstrated marked regression of peritoneal mucin accumulation and implants, accompanied by normalization of tumor markers. In addition, there was significant improvement of the patient's condition.

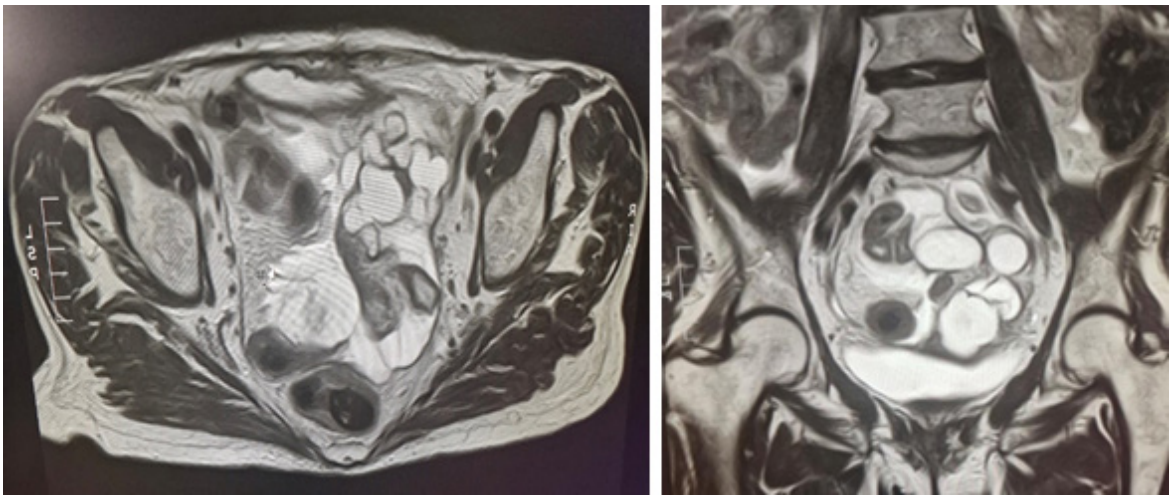

Figure 1. Initial MRI scan indicating multiple peritoneal deposits of cystic characteristics, most likely of mucinous composition (along the peritoneum, bowel serosa, and hepatic capsule). Presence of free fluid and/or mucinous accumulations in the peritoneal recesses.

Maintenance therapy with bevacizumab plus 5-FU/LV was continued, resulting in prolonged stable disease. The patient has been followed up routinely to evaluate the treatment efficacy and to monitor the adverse effects.

After a total of 32 cycles of bevacizumab plus chemotherapy, the patient developed vaginal discharge and fecal passage through the vagina. Gynecologic examination confirmed an enterovaginal fistula, while follow-up CT and MRI showed no disease progression (Figure 2).

Because of impaired quality of life, the patient was referred for surgical management. Intraoperatively, the surgical team assessed that complete cytoreduction was technically feasible. The metastatic deposits identified on the peritoneum were limited in number and distribution. Based on this intraoperative assessment, the decision was made to proceed with cytoreductive surgery combined with fistulectomy. The goal of the intervention was

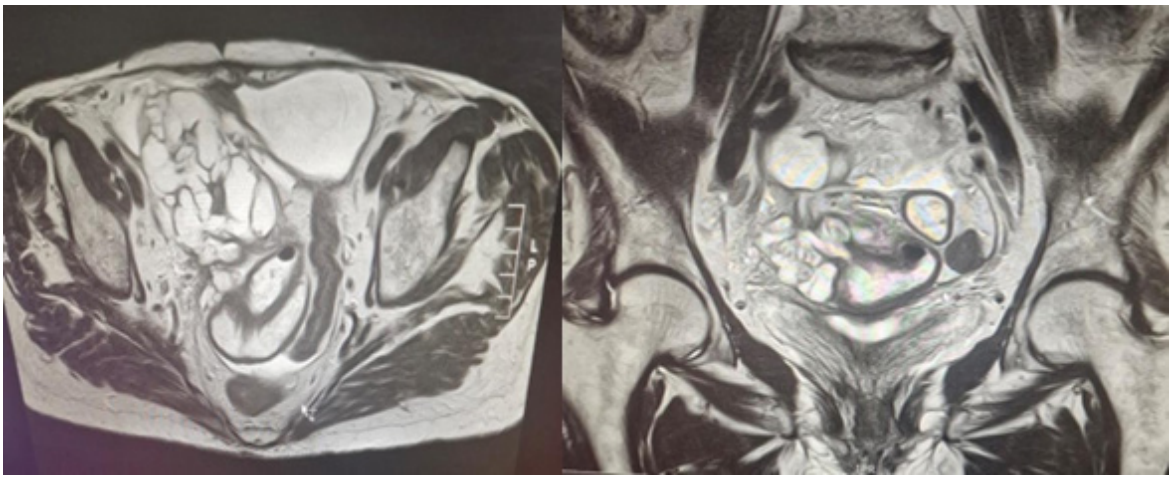

Figure 2. MRI scan indicating cystic pelvic tumor originating from the appendix, with a suspected fistulous connection.

to achieve macroscopic disease clearance and to improve the patient's quality of life by resolving the fistula-related symptoms.

Postoperative imaging showed no evidence of disease. The patient remains progression-free for nearly three years, and disease-free for one year.

DISCUSSION

Cytoreductive surgery and HIPEC are established treatments for surgically resectable appendiceal adenocarcinomas, although such cases are rare and challenging to manage. For patients with unresectable disease, systemic chemotherapy is considered; however, prospective data confirming benefit are lacking due to the rarity of the disease. HIPEC was not performed in this case due to the initial emergency presentation and inoperable disease status.

Bevacizumab, a monoclonal antibody targeting VEGF, is approved in combination with chemotherapy as first-line therapy for metastatic CRC (6,7). Recent retrospective data suggest improved overall and progression-free survival in patients with unresectable appendiceal epithelial neoplasms treated with bevacizumab plus chemotherapy (8).

Considering these findings and the absence of contraindications, we initiated bevacizumab + FOLFOX therapy for 12 cycles. Given both radiologic (progression-free interval of two years) and clinical responses, we continued maintenance treatment with bevacizumab + 5-FU/LV for 20 additional cycles, with regular follow-up for efficacy and toxicity monitoring.

After a total of 32 cycles, therapy was discontinued following the development of an enterovaginal fistula, a known complication of bevacizumab use. According to the current recommendations of the manufacturer and international oncology guidelines (9,10), the development of a fistula of any type is an absolute contraindication for further bevacizumab therapy, which must be permanently discontinued.

In our patient, following the discontinuation of bevacizumab, surgical management was pursued due to symptomatic fistula and acceptable disease control. Intraoperatively, complete cytoreduction was achievable, and CRS with fistulectomy was successfully performed.

The patient achieved complete remission, remains progression-free for three years, and disease-free for one year, highlighting the potential role of multimodal therapy even in initially inoperable cases.

CONCLUSION

This case highlights the potential for long-term survival in initially inoperable patients with advanced mucinous appendiceal adenocarcinoma and peritoneal carcinomatosis when treated with combined cytoreductive surgery and bevacizumab plus chemotherapy. Individualized, multidisciplinary treatment strategies may significantly improve outcomes in this rare malignancy.

CONFLICT OF INTEREST AND FUNDING

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