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Comprehensive genomic profiling-guided treatment selection in appendiceal adenocarcinoma with discordant mismatch repair findings: a case report and literature review

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Case Report

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Abstract

Background

Appendiceal adenocarcinoma is rare, and systemic treatment is often extrapolated from colorectal cancer. Discordance between mismatch repair (MMR) immunohistochemistry and microsatellite instability (MSI) or tumor mutational burden (TMB) testing can complicate treatment selection, particularly in rare gastrointestinal cancers. We report a case in which comprehensive genomic profiling (CGP) helped interpret discordant MMR findings and guide subsequent treatment.

Case presentation:

A 25-year-old woman presented with advanced appendiceal signet-ring cell adenocarcinoma with bilateral ovarian metastases and peritoneal dissemination. MMR immunohistochemistry showed loss of MLH1/PMS2 expression, whereas MSI testing and tumor-normal paired CGP showed microsatellite-stable disease and low TMB. Nivolumab plus ipilimumab was not effective, and ascites persisted after mFOLFOX6 alone. CGP revealed *RAS*/*BRAF* V600E wild-type and HER2-negative status without apparent major anti-EGFR resistance-associated alterations, and also identified a germline *TP53* pathogenic variant consistent with Li-Fraumeni syndrome. After panitumumab was added to mFOLFOX6, the patient achieved a marked clinical improvement and a partial response, with sustained disease control at the time of writing.

Conclusions

This case suggests that MMR protein loss on immunohistochemistry alone may not define the dominant therapeutic biology of a tumor when MSI and TMB results are discordant. Integrating MMR immunohistochemistry, MSI status, TMB, and CGP may support treatment selection in rare gastrointestinal cancers and may reveal clinically important germline findings.

Background

Appendiceal signet-ring cell carcinoma is an extremely rare and highly aggressive subtype of gastrointestinal malignancy that accounts for < 0.1% of all gastrointestinal tumors and approximately 4%–5% of all primary appendiceal carcinomas [1, 2]. Current evidence regarding systemic therapies for this type of cancer remains limited; hence, treatment strategies for unresectable or metastatic appendiceal adenocarcinoma are often extrapolated from those established for colorectal cancer based on its anatomical and histological proximity to colorectal cancer. Fluoropyrimidine- and oxaliplatin-based regimens, including mFOLFOX6 or CAPOX, have commonly been used in clinical practice; however, prospective data specific to appendiceal adenocarcinoma have been scarce, with the optimal integration of molecularly targeted agents remaining unclear [3, 4, 5].

Systemic therapy for metastatic colorectal cancer has been increasingly guided by molecular biomarkers, including *RAS* and *BRAF* V600E mutation, HER2 overexpression and/or amplification status, microsatellite instability (MSI) or mismatch repair (MMR) deficiency, tumor mutational burden (TMB), and gene fusions involving *NTRK*, *ALK*, *RET*, or *ROS1* [3, 4]. MSI-high or MMR-deficient tumors are generally considered sensitive to immune checkpoint inhibitors, whereas *RAS*/*BRAF* V600E wild-type status tumors can benefit from anti-EGFR antibody-based therapies. Nevertheless, the direct application of these biomarker-driven strategies to appendiceal adenocarcinoma requires caution given the biological differences between appendiceal tumors and colorectal cancer and the lack of prospective clinical trials on appendiceal tumors [6, 7].

Among these biomarkers, MMR deficiency detected via immunohistochemistry has been deemed clinically important; however, MSI results and MMR deficiency testing do not always match exactly [8]. In fact, recent studies have reported a 3%–10% discordance between these two tests [9]. In particular, discordance between MMR immunohistochemistry and MSI or TMB status can complicate treatment selection. When MMR deficiency is accompanied by microsatellite-stable (MSS) status and low TMB, the biological and therapeutic implications of MMR protein loss may differ from those of canonical MSI-high, hypermutated tumors. In such settings, comprehensive genomic profiling (CGP) may provide essential information for interpreting discordant biomarker findings and selecting subsequent systemic therapy.

CGP can be utilized to simultaneously assess MSI status, TMB, oncogenic drivers, and resistance-associated alterations. Furthermore, tumor and normal paired panels can be used to identify germline pathogenic variants [10]. In *RAS* wild-type metastatic colorectal cancer, the concept of negative hyperselection has emerged as a strategy for identifying patients who may derive greater benefit from anti-EGFR antibody therapy by excluding tumors harboring alterations associated with primary resistance, such as *RAS*, *BRAF* V600E, *PTEN*, *EGFR* extracellular domain alterations, *HER2* or *MET* amplification, and selected oncogenic fusions [11, 12]. Although this concept has not been validated specifically in appendiceal adenocarcinoma, it may provide a rational framework for treatment selection in selected patients with *RAS* wild-type appendiceal tumors, particularly when standard biomarkers show inconclusive results.

The present case illustrates the clinical relevance of this integrated approach. Although MMR immunohistochemistry showed MLH1/PMS2 loss, MSI testing and CGP revealed MSS and low TMB. Furthermore, CGP provided broader molecular information that helped guide treatment selection beyond MMR-deficient status, which facilitated the identification of a germline *TP53* pathogenic variant consistent with Li-Fraumeni syndrome. This case therefore highlights the importance of interpreting MMR deficiency in the context of MSI, TMB, and CGP results rather than assuming that MMR protein loss alone defines the dominant therapeutic biology of the tumor.

Case presentation

A 25-year-old woman with no significant medical history presented to a clinic with progressive abdominal distension after having experienced abdominal pain several months earlier. Contrast-enhanced computed tomography (CT) subsequently revealed bilateral ovarian masses and multiple peritoneal nodules with massive ascites. She was then referred to the gynecology department of our hospital with a suspected diagnosis of ovarian cancer.

A biopsy specimen obtained from the uterine cervix at the referring hospital revealed adenocarcinoma, with immunohistochemical findings suggesting an intestinal origin. The differential diagnosis included primary ovarian cancer with cervical involvement and Krukenberg tumor arising from a gastrointestinal malignancy. On admission, her abdomen was distended but soft, with tenderness and a palpable mass in the right lower quadrant. Laboratory testing showed an inflammatory response (C-reactive protein, 16.62 mg/dL) and hypoalbuminemia (albumin, 1.3 g/dL). Serum tumor markers were moderately elevated, including carcinoembryonic antigen (56.2 ng/mL) and carbohydrate antigen 125 (128 U/mL).

Contrast-enhanced CT showed extensive peritoneal dissemination centered around the appendix and bilateral ovarian tumors (Fig. 1a, b). Colonoscopy suggested findings of submucosal tumor extension around the appendiceal orifice (Fig. 1c, d). Biopsy specimens from this lesion showed adenocarcinoma with signet-ring cell features in the submucosal layer (Fig. 1e, f). Immunohistochemistry demonstrated positivity for CK20 and CDX2 (Fig. 1g, h) and negativity for CK7 and PAX8, supporting a gastrointestinal origin. Given that the ovarian tumors were symptomatic and clinically important for diagnosis, bilateral oophorectomy was performed. Subsequent examination of the resected ovarian tumors revealed histological and immunohistochemical features similar to those of the cervical and appendiceal lesions, confirming metastatic appendiceal adenocarcinoma. A final clinical diagnosis of advanced appendiceal signet-ring cell adenocarcinoma with peritoneal, ovarian, and uterine cervical involvement was established.

MMR immunohistochemistry showed consistent loss of MLH1 and PMS2 expression (Fig. 2a, b) but retention of MSH2 and MSH6 expression (Fig. 2c, d). Based on these findings, the tumor was initially considered to be MMR-deficient. However, MSI testing subsequently showed MSS disease. Additional tumor and normal paired CGP using GenMineTOP revealed MSS status and a low TMB of 3.7 mutations/Mb. The tumor was *RAS*/*BRAF* V600E wild-type and HER2-negative. GenMineTOP identified several genomic alterations including a *TP53* variant (NM_000546: c.743G > A, p.R248Q) in the tumor sample (Table 1). Subsequent tumor-normal paired panel analysis demonstrated that the variant was also present in the non-tumor sample with a variant allele frequency (VAF) of 46.8%, confirming its germline origin. The pathogenicity of this variant was classified as pathogenic in the ClinVar database, confirming a genetic diagnosis of Li-Fraumeni syndrome. The diagnosis also had important implications for family counseling. Targeted single-site germline testing for the *TP53* variant was performed in both parents, with neither parent carrying the variant. These findings suggested that the *TP53* variant in this patient was apparently de novo, highlighting that CGP may identify Li-Fraumeni syndrome even in the absence of a typical familial phenotype.

Table 1
Genome profiling and MSI testing

Biomarker	
Microsatellite status	MSS
	MSS (PCR-based molecular testing)
Tumor mutation burden	Low
	3.7 Mutations/Mb

Gene	RefSeq Transcript	Nucleotide change	Protein change	VAF	Location (GRCh38)
CTNMA1	NM_001903	c.1351C > T	p.R451*	34.1%	chr5:138904403
EPHA7	NM_004440	c.2937C > A	p.S979R	27.2%	chr6:93243486
FGFR2	NM_000141	c.1144T > C	p.C382R	26.4%	chr10:121515260
PARP4	NM_006437	c.4949T > C	p.L1650P	12.5%	chr13:24426496
PIK3R3	NM_003629	c.1093C > G	p.R365G	*22.2%*	chr1:46046012
PTPRD	NM_002839	c.2504A > G	p.Q835R	23.6%	chr9:8486313
RNF43	NM_017763	c.857G > A	p.R286Q	32.0%	chr17:58360244
TP53	NM_000546	c.743G > A	p.R248Q	67.1%	chr17:7674220

Abbreviations: MSI, microsatellite instability; MSS, microsatellite stable; PCR, polymerase chain reaction; VAF, variant allele frequency; GRCh, Genome Reference Consortium human

Given that MMR immunohistochemistry showed MMR deficiency, systemic therapy with nivolumab plus ipilimumab was initiated according to treatment strategies for unresectable colorectal cancer. However, after three cycles of this treatment, the patient showed radiological progression, with increasing ascites requiring drainage. These findings were clinically consistent with the discordant biomarker profile of MMR deficiency on immunohistochemistry but MSS and low TMB on MSI testing and CGP. Therefore, mFOLFOX6 was administered as second-line therapy. However, the patient's ascites did not decrease even after two cycles of mFOLFOX6, which necessitated repeat ascites drainage. The treatment strategy was therefore reconsidered based on the integrated biomarker results. Given the *RAS*/*BRAF* V600E wild-type status, HER2 negativity, and the absence of apparent major anti-EGFR resistance-associated alterations on CGP, panitumumab was added to mFOLFOX6. After initiating mFOLFOX6 plus panitumumab, the patient achieved marked clinical improvement. Subsequent magnetic resonance imaging showed decreased ascites and abdominal nodule shrinkage (Fig. 3b), with the best overall response being partial response according to RECIST criteria. At the time of writing, the patient had

received 10 additional cycles of mFOLFOX6 plus panitumumab, with sustained disease control and preserved treatment tolerability (Fig. 3a).

This clinical course illustrates the importance of interpreting MMR in the context of MSI status, TMB, and broader CGP findings. In rare gastrointestinal cancers, such as appendiceal adenocarcinoma, CGP may provide clinically relevant information for treatment selection, particularly when standard biomarkers show discordant results.

Patient perspective

A separate patient-perspective statement was not collected. Written informed consent was obtained from the patient for publication of this case report and accompanying clinical information and images.

Discussion and Conclusions

The present case emphasizes several important issues in the management of rare gastrointestinal cancers in the era of precision oncology. First, appendiceal adenocarcinoma, particularly signet-ring cell carcinoma, can present with extensive peritoneal dissemination and bilateral ovarian metastases, mimicking a primary gynecological malignancy. Second, MMR deficiency detected through immunohistochemistry does not always fully reflect the molecular phenotype relevant to immune checkpoint inhibitor sensitivity, especially when MSI testing and CGP show MSS and low TMB. Third, CGP can provide clinically significant information beyond standard biomarker testing by integrating MSI status, TMB, oncogenic alterations, resistance-associated genomic features, and potential germline findings. This integrated interpretation allowed us to reconsider the initial immune checkpoint inhibitor-based strategy in the present case and adopt another treatment approach with mFOLFOX6 plus panitumumab, which resulted in marked clinical improvement and sustained disease control.

Given the rarity of appendiceal adenocarcinoma, its optimal systemic treatment remains insufficiently defined [1, 2]. In clinical practice, the treatment of appendiceal adenocarcinoma is often extrapolated from methods used for metastatic colorectal cancer given the anatomical proximity and histopathological similarities [3, 4]. However, appendiceal tumors have distinct biological features, and confirmed evidence for the use of molecularly targeted therapies in this disease has been limited [5]. Signet-ring cell adenocarcinoma, which is particularly aggressive, has been frequently associated with advanced-stage disease, peritoneal dissemination, and poor prognosis. Although cytoreductive surgery with HIPEC has been associated with improved survival outcomes in patients with signet-ring cell adenocarcinoma, confirmatory clinical trials have been lacking [13, 14]. In the present case, the patient presented with massive ascites, bilateral ovarian tumors, and peritoneal nodules, for which our initial clinical suspicion was ovarian cancer. The combination of endoscopic findings around the appendiceal orifice and immunohistochemistry showing CK20 and CDX2 positivity with CK7 and PAX8 negativity was critical for identifying a gastrointestinal origin. This diagnostic process emphasizes the importance of

considering appendiceal or colorectal origin in young women with bilateral ovarian tumors and peritoneal dissemination, particularly when pathological findings suggest intestinal differentiation.

A critical feature observed in the present case was the discordance between MMR immunohistochemistry and MSI/TMB status. Immunohistochemistry showed loss of MLH1 and PMS2 expression, initially suggesting MMR deficiency [15]. Based on this finding, immune checkpoint blockade was considered a rational therapeutic option according to treatment strategies for unresectable MMR-deficient colorectal cancer. Indeed, the CheckMate 8HW trial showed that nivolumab plus ipilimumab demonstrated superior progression-free survival compared to chemotherapy or nivolumab as first-line treatment for MSI-high or MMR-deficient metastatic colorectal cancer [16, 17]. However, subsequent MSI testing showed MSS disease, with CGP also demonstrating MSS status with low TMB. Unfortunately, the tumor did not respond to nivolumab plus ipilimumab, and radiological progression with increasing ascites was observed. The clinical course of the current case seemed to suggest that MLH1/PMS2 loss on immunohistochemistry did not represent a canonical MSI-high, hypermutated phenotype.

Discordance between MMR immunohistochemistry and MSI testing has been reported in several tumor types, including colorectal cancer, and may arise from multiple mechanisms. Several studies have reported a 3%–10% discordance rate between these two tests [18, 19, 20, 21, 22, 23]. Moreover, a recent clinical trial showed that 18% of patients with locally detected MMR-deficient or MSI-high colorectal cancer were not confirmed to have MMR deficiency/MSI-high status by central laboratory testing [16]. Potential explanations include technical or pre-analytical factors, low tumor cellularity [24], pre-analytical difficulties [25], physician skills [26], neoadjuvant treatment [27], intratumoral heterogeneity [28], and differences in the sensitivity and specificity of the assays used [9]. In the present case, the patient did not receive any chemotherapy before undergoing both MMR immunohistochemistry and MSI testing using the surgically resected ovarian metastatic specimens. Furthermore, immunohistochemistry did not show heterogeneous loss of MLH1/PMS2 expression, while CGP testing did not detect any pathogenic variant in *MLH1*. Therefore, aberrant methylation of the *MLH1* promoter region could be one possible mechanism; however, *MLH1* promoter methylation was not assessed in this case. Moreover, loss of MMR protein expression may not always be accompanied by sufficient functional consequences to generate MSI-high status or high TMB [29]. Therefore, although MMR deficiency on immunohistochemistry is a clinically important biomarker, it might have been a secondary or biologically non-canonical event that did not lead to a tumor-wide MSI-high or hypermutated phenotype.

The CGP findings in the present case played a pivotal role in suggesting that the biological and therapeutic implications of MMR protein loss might differ from those of typical MSI-H/MMR-deficient colorectal cancer. CGP testing did not reveal apparent major genomic alterations associated with primary resistance to anti-EGFR antibody therapy. In metastatic colorectal cancer, anti-EGFR antibody therapy has generally been considered for *RAS*/*BRAF* wild-type tumors, particularly those arising from the left colon [30, 4]. Right-sided primary tumors are generally less responsive to anti-EGFR therapy, due in part to the increased frequency at which they harbor molecular features associated with resistance, including *BRAF* V600E mutations, HER2 or *MET* amplification, *PTEN* pathway alterations, *EGFR*

extracellular domain alterations, and *ALK*, *RET*, and *NTRK1* fusions. Indeed, the phase 3 PARADIGM trial, which evaluated the association between circulating tumor DNA (ctDNA) of these gene alterations and efficacy outcomes, revealed that overall survival was longer with panitumumab plus modified mFOLFOX6 than with bevacizumab plus modified mFOLFOX6 among patients with ctDNA lacking gene alterations in the panel, regardless of tumor sidedness [11]. Therefore, the strategy of negative hyperselection has emerged to refine patient selection for anti-EGFR antibody therapy by excluding such resistance-associated alterations, although CGP testing in the present case was not based on ctDNA. The patient subsequently achieved marked clinical improvement, with near disappearance of ascites and sustained disease control after 10 additional cycles of treatment. Importantly, this favorable response should be associated with mFOLFOX6 plus panitumumab combination therapy. However, the individual contribution of panitumumab cannot be determined from a single case. Nevertheless, the clinical course suggests that CGP-based integrated biomarker interpretation may help identify therapeutic opportunities even in right-sided or appendiceal *RAS* wild-type tumors, which have less clearly defined standard treatment protocols.

Another important aspect of CGP in the present case was the identification of a germline *TP53* pathogenic variant, which confirmed the diagnosis of Li-Fraumeni syndrome, a hereditary cancer predisposition syndrome caused by germline pathogenic variants in *TP53*. This syndrome has been associated with a broad tumor spectrum, including breast cancer, sarcoma, brain tumors, adrenocortical carcinoma, and other malignancies [31]. Recently, studies have reported germline *TP53* variants in a subset of patients with young-onset colorectal cancer, although colorectal and appendiceal cancers are not classical core tumors of Li-Fraumeni syndrome [32, 33]. Another study showed that among 457 early-onset colorectal cancer patients, 6 (1.3%; 95% CI, 0.5%–2.8%) carried germline missense *TP53* alterations, none of whom met the clinical criteria for Li-Fraumeni syndrome [34]. With the growing use of CGP, clinicians have increasingly faced challenges in interpreting the biological and clinical significance of germline *TP53* variants in families whose phenotypes are atypical for Li-Fraumeni syndrome.

Identifying the specific *TP53* variant may also provide additional biological information. Indeed, research has shown that distinct hotspot *TP53* mutants exert different phenotypes in colorectal cancer and that *TP53* p.R248Q and p.R248W share biological features with *TP53* p.R273H, including enrichment of a p.R273-associated transcriptional signature linked to aggressive tumor behavior and poorer outcomes [35]. Although these findings were derived from colorectal cancer and cannot be directly extrapolated to appendiceal adenocarcinoma, they suggest that CGP may provide not only diagnostic information for hereditary cancer syndromes but also potentially relevant information regarding tumor phenotype and prognosis. The diagnosis of Li-Fraumeni syndrome in the present case had important clinical implications beyond treatment selection, including genetic counseling, discussion of predictive testing for relatives, and consideration of radiation exposure.

Several limitations should be acknowledged. First, given that this was a single-case observation, our findings cannot be generalized to all patients with appendiceal adenocarcinoma or MMR deficiency/MSS

discordance. Second, considering that a favorable response occurred after treatment with mFOLFOX6 plus panitumumab, the specific contribution of anti-EGFR antibody therapy cannot be isolated. Third, direct evidence supporting anti-EGFR antibody therapy in appendiceal adenocarcinoma remains limited, and the concept of negative hyperselection has been developed mainly in metastatic colorectal cancer. Fourth, the mechanism underlying the discordance between MMR immunohistochemistry and MSI/TMB results remains unclear.

In conclusion, this case highlights the importance of integrating MMR immunohistochemistry with MSI testing, TMB assessment, and CGP findings when selecting systemic therapy for rare gastrointestinal cancers. In tumors showing discordant MMR-deficient and MSS/low TMB findings, MMR deficiency detected via immunohistochemistry alone may not fully define the dominant therapeutic biology. CGP may help reinterpret discordant biomarker results, identify alternative treatment strategies (e.g., anti-EGFR therapy) in selected *RAS* wild-type tumors, and uncover clinically important germline findings, such as Li-Fraumeni syndrome. This integrated approach may be particularly valuable in rare malignancies, such as appendiceal adenocarcinoma, for which disease-specific evidence remains limited.

Abbreviations

CA125, carbohydrate antigen 125; CAPOX, capecitabine plus oxaliplatin; CEA, carcinoembryonic antigen; CGP, comprehensive genomic profiling; CK, cytokeratin; CT, computed tomography; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HIPEC, hyperthermic intraperitoneal chemotherapy; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI, microsatellite instability; MSS, microsatellite stable; PAX8, paired box 8; RECIST, Response Evaluation Criteria in Solid Tumors; TMB, tumor mutational burden; VAF, variant allele frequency.

Declarations

Ethics approval and consent to participate

The Research Ethics Committee of Toyama University Hospital approved publication of this case report (approval no. R2025039). Consent to participate was not applicable to this case report.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying clinical information and images.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Not applicable.

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Author Contribution

TA wrote the original manuscript. YT, YNo, TM, RF, YNa, IM, KT, MS, YU, SK, KH, and IY contributed to data collection, interpretation of clinical and pathological findings, and preparation of the figures. All authors read and approved the final manuscript.

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Availability of data and materials

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

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Figures

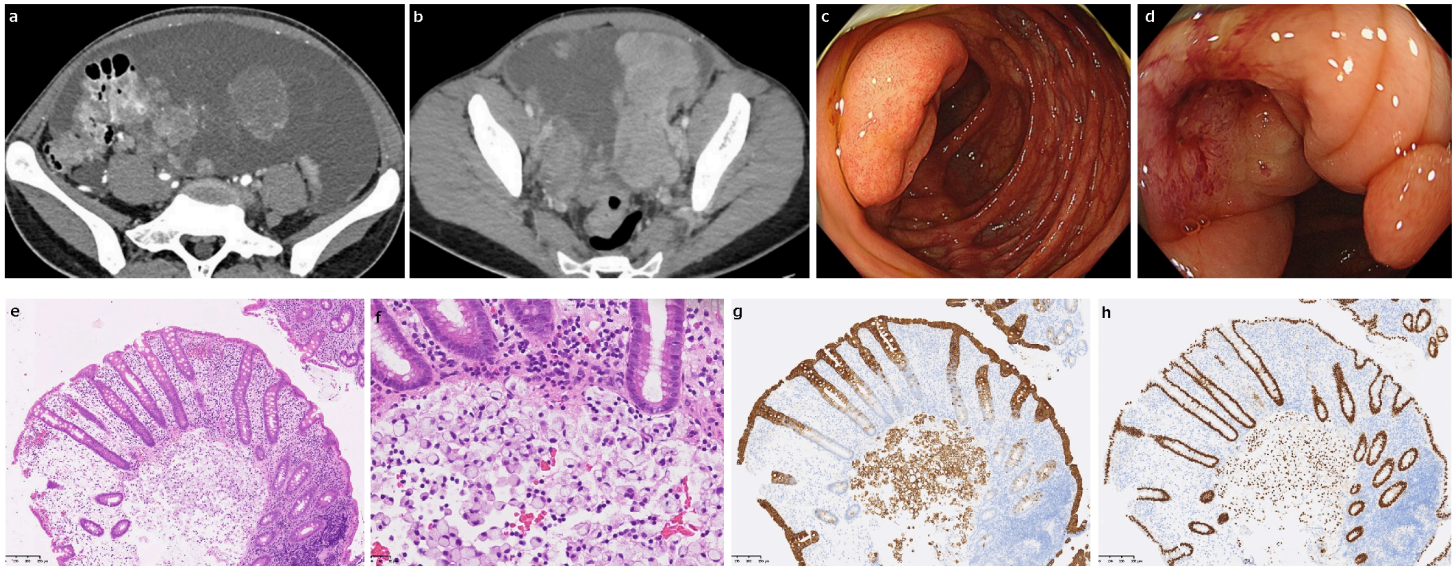


Figure 1

Computed tomography, colonoscopic, histopathological, and immunohistochemical findings at diagnosis. a, b Contrast-enhanced computed tomography images showing extensive peritoneal dissemination centered around the appendix, massive ascites, and bilateral ovarian tumors. c, d Colonoscopy images showing a submucosal tumor-like lesion and mucosal abnormalities around the appendiceal orifice. e, f Hematoxylin and eosin staining of a biopsy specimen from the appendiceal lesion showing adenocarcinoma with signet-ring cell features in the submucosal layer. g, h Immunohistochemical staining showing positivity for CK20 (g) and CDX2 (h), supporting a gastrointestinal origin.

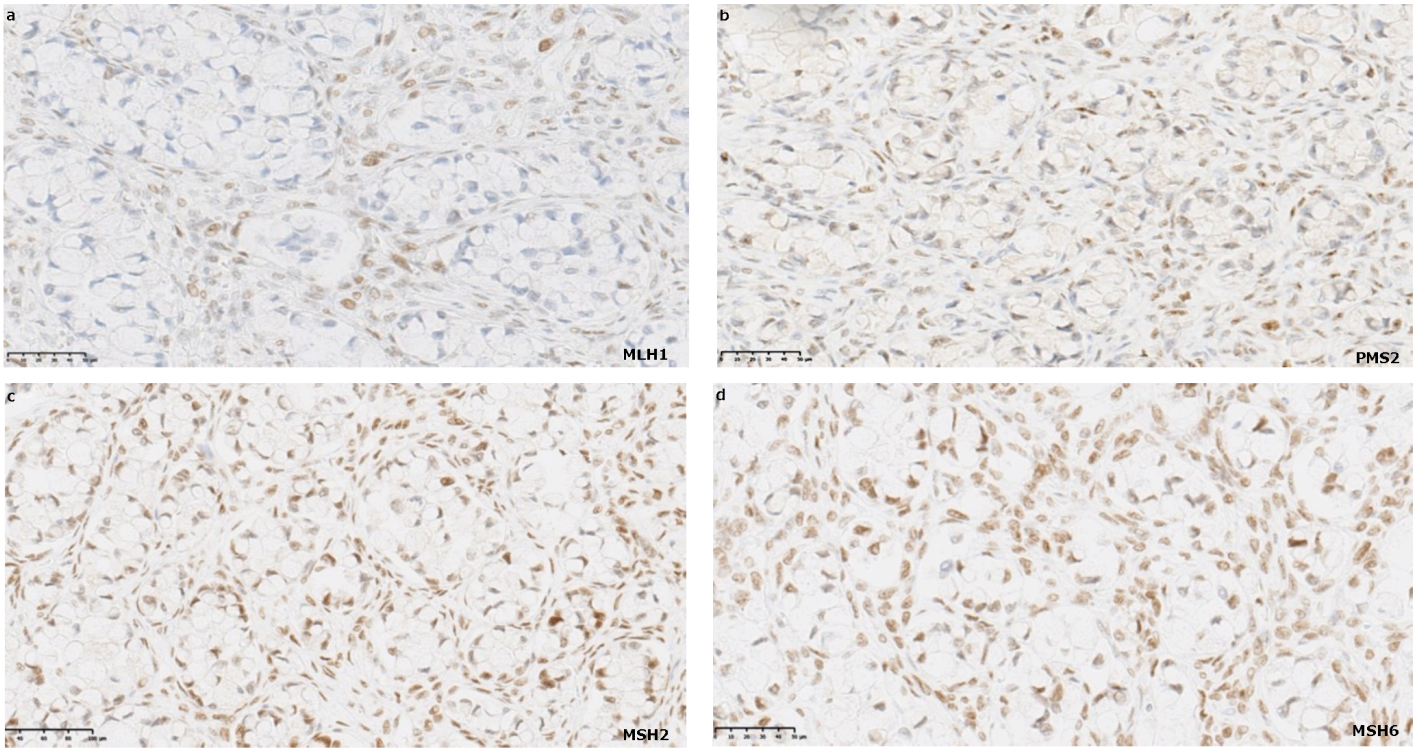


Figure 2

Immunohistochemical analysis of mismatch repair proteins. Tumor cells showed loss of nuclear expression of MLH1 (a) and PMS2 (b), but retention of MSH2 (c) and MSH6 (d). These findings initially suggested deficient mismatch repair.

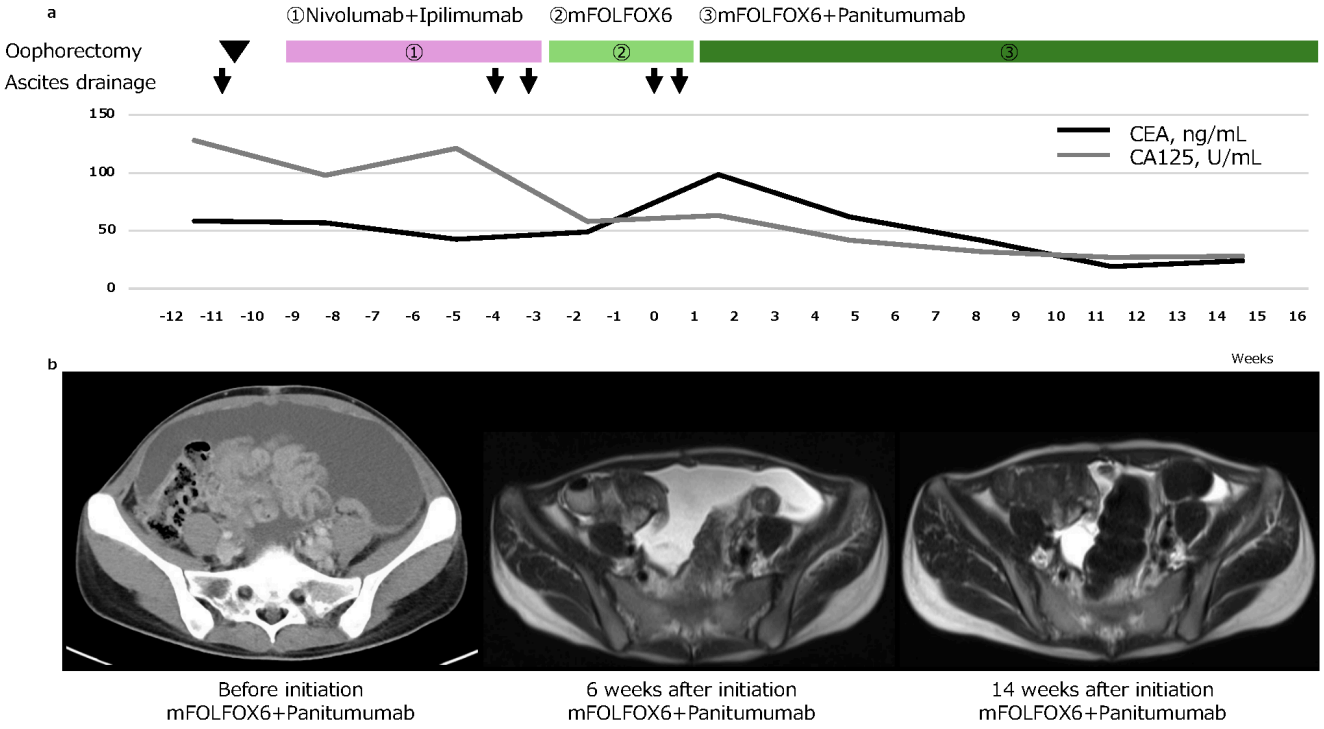


Figure 3

Clinical course and radiological response to systemic therapy. a Timeline of systemic therapies, oophorectomy, ascites drainage, and serial tumor marker levels. The patient initially received nivolumab plus ipilimumab, followed by mFOLFOX6 and then mFOLFOX6 plus panitumumab. b Representative radiological images before initiation and 6 and 14 weeks after initiation of mFOLFOX6 plus panitumumab showing a decrease in ascites and abdominal lesions. CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125.