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Case Report

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Not Complete Pathologic Response but Hyperprogression as Better Response in dMMR/MSI-H Locally Advanced Rectal Cancer: A Case Report

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Abstract

Introduction

Neoadjuvant PD-1 blockade has recently transformed the management of mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) locally advanced rectal cancer, allowing organ preservation in selected patients. However, real-world responses may be more heterogeneous than initially reported.

Case Report

We report a 32-year-old woman with Lynch syndrome–associated dMMR/MSI-H locally advanced rectal adenocarcinoma (cT4bN+M0) treated with neoadjuvant dostarlimab. Shortly after treatment initiation, the patient developed rapid local tumor enlargement complicated by necrosis, abscess formation, fistulization and intestinal obstruction requiring emergency surgical procedures. Initial imaging suggested pseudoprogression; however, subsequent assessments demonstrated aggressive tumor growth consistent with hyperprogressive disease.

Discussion

Hyperprogressive disease is an uncommon but clinically relevant response pattern associated with immune checkpoint inhibitors and poses major diagnostic challenges, particularly in distinguishing it from pseudoprogression. This case highlights the limitations of MSI/MMR status alone as a predictive biomarker for response.

Conclusion

Improved biomarkers, refined radiological criteria and early multidisciplinary reassessment are needed to optimize patient selection and management during neoadjuvant immunotherapy for dMMR/MSI-H rectal cancer.

Introduction

Rectal cancer is a complex disease that requires a multidisciplinary approach. In locally advanced stages, standard management includes a combination of neoadjuvant radiotherapy and chemotherapy, followed by surgery. However, this approach is highly invasive and can lead to significant side effects, including bowel, urinary and sexual dysfunction, as well as infertility in patients potentially cured [1]. Additionally, these patients often require a diverting colostomy, which can have an important impact on their quality of life [2]. Given these challenges, recent efforts have focused on identifying patients who could benefit from a de-escalation strategy. It is now well established that a subset of patients with microsatellite instability-high (MSI-H) tumors are particularly responsive to immunotherapy.

Approximately 5 to 10% of rectal adenocarcinomas are mismatch-repair deficient [3]. In patients with MSI-H metastatic colo-rectal cancer, immunotherapy is already an established treatment, with clear evidence of efficacy [4], whereas its role in the locally advanced setting remained uncertain. The need to achieve cure with systemic therapy alone, thereby preserving the organ, led to the study by Cercek et al., published in The New England Journal of Medicine in 2022. This phase II study demonstrated that in patients with mismatch repair–deficient locally advanced rectal cancer, neoadjuvant PD-1 blockade alone with Dostarlimab resulted in a clinical and radiological complete response in all patients who had at least six months of follow-up. These patients could then be managed with surveillance alone, avoiding surgery. This study has completely changed the treatment paradigm for rectal cancer in the locally advanced setting. Dostarlimab, a well-established drug widely used in other solid tumors, is considered a safe therapy, with adverse events rarely exceeding grade 2 and often manageable with oral medication. The study reported no treatment-related adverse events of grade 3 or higher [3]. The case presented is particularly relevant as it highlights an unexpected issue of hyperprogression and poor response in a clinical scenario that otherwise closely mirrors the study population.

Case Report

A 32-year-old woman was admitted to the gastroenterology department of our hospital complaining of abdominal pain and profuse diarrhea with the presence of mucus and blood in the stool. The patient denied any comorbidities but reported a family history of Lynch syndrome, which affected both her mother and maternal grandmother.

A total colonoscopy was performed, revealing a lesion in the rectum approximately 5 cm from the external anal margin, occupying two-thirds of the lumen with a substenosing pattern and extending for approximately 14 cm. Histological examination of biopsies specimens confirmed an ulcerated adenocarcinoma of the large intestine. Immunohistochemical investigations showed no

alteration of the DNA Mismatch Repair (MMR) complex.

A WB CT scan did not reveal secondary disease localizations. An abdominal MRI showed a lesion starting from the anorectal junction, occupying two-thirds of the lumen with a substenosing pattern, extending for approximately 14 cm, measuring approximately 7 cm × 8 cm (LL × AP), with internal necrotic aspects. The lesion had no clear cleavage plane with the mesorectal fascia and the posterior vaginal wall. Additionally, the MRI showed pericentimetric lymph nodes in the locoregional and obturator regions. According to the eighth edition of the Union for International Cancer Control TNM system, the patient's clinical stage was defined as cT4b cN+ cM0, based on direct invasion of surrounding structures and the presence of pathological locoregional lymph nodes [5] (Figure 1A).

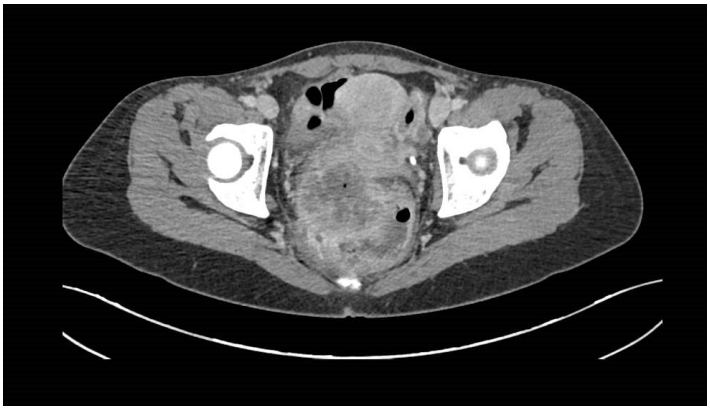

Figure 1A: **Computed tomography (CT) findings during treatment**: **(A)** Baseline contrast-enhanced abdominal CT scan showing a large rectal mass with irregular margins and internal necrotic areas, without evidence of distant metastases.

Tumor marker assays (CEA, CA 19-9) were performed and resulted negative. Given the strong correlation between Lynch syndrome and microsatellite instability in colorectal cancer and considering the patient's family history, the initial immunohistochemical finding of MMR proficiency was considered potentially misleading [6, 7]; therefore, a PCR-based analysis was requested to further assess microsatellite status. This analysis revealed MSI-High status (according to the Idylla technique which detected mutations in all the analyzed genes [ACVR2A, BTBD7, DIDO1, MRE11, RYR3, SULF2] except for SEC31A). Subsequent revision of the immunohistochemical analysis demonstrated loss of MLH1 and PMS2 expression with preserved MSH2 and MSH6, consistent with a primary MLH1 deficiency. Germline genetic testing ultimately identified a pathogenic splice-site variant in MLH1. No additional pathogenic variants in other mismatch repair genes were reported.

After a tumor board discussion, considering the molecular findings, immunotherapy was started with Dostarlimab 500 mg IV on day 1 every 21 days for a total of 6 months. The patient started therapy on September 19, 2024.

After two cycles of immunotherapy, the patient was admitted to the oncology department due to intestinal obstruction, pain and hyperpyrexia (October 15-29, 2024). An abdominal CT scan (October 15, 2024) showed an increase in the rectal mass volume, with more extensive necrotic aspects and formation of an abscess. A possible fistulous tract connecting to the vaginal ostial region was suspected. Additionally, there was an increase in the size of some locoregional lymph nodes (Figure 1B).

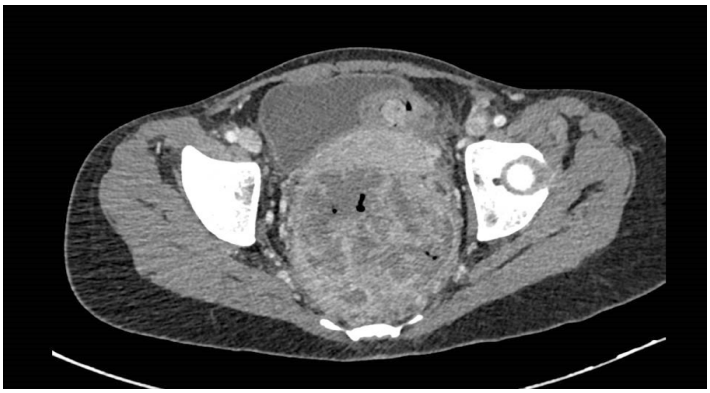

Figure 1B: CT scan performed after two cycles of dostarlimab demonstrating marked increase in tumor size, with extensive necrosis, abscess formation, and suspected fistulous tract toward adjacent structures, consistent with early atypical radiological progression.

As a result, the patient underwent an emergency end colostomy on October 18, 2024 (peritoneal washing negative for neoplastic cells).

On the second postoperative day, due to the onset of acute abdomen, the patient underwent a new abdominal CT scan. Surgical evaluation concluded that no emergency surgical intervention would provide meaningful clinical benefit in that setting.

In the setting of a rapidly deteriorating clinical condition requiring high-dose opioids to control cancer pain, the observed unusual response to immunotherapy, the patient's strong refusal of demolitive surgery and the need for prompt disease control, a switch to systemic chemotherapy was considered the most appropriate therapeutic strategy. We decided to start salvage therapy with mFOLFIRINOX. Treatment was started with a 50% dose reduction, taking into account both the patient's clinical status and known pharmacogenetic variants (DPYD mutation with

a recommended dose intensity of 85% and UGT1A mutation with a recommended dose intensity of 70%). This decision was further supported by the intention to achieve rapid stabilization while preserving future local treatment options, in line with available evidence and the patient's expressed preferences.

On November 2, 2024, due to uncontrolled abdominal pain, the patient underwent another abdominal CT scan, which raised suspicion of intestinal perforation and showed a slight increase in the pelvic mass.

Due to CT findings, the patient underwent an emergency xiphopubic laparotomy, which revealed dehiscence of the rectal stump suture and diffuse purulent contamination of the abdominal cavity. Extensive peritoneal lavage was performed, the rectal stump was closed, the distal colonic loop was resected, a terminal colostomy was created, and an abdominal drain was placed and the patient was treated with antibiotic therapy. After an initial clinical improvement, persistent purulent drainage required the initiation of vacuum-assisted closure (VAC) therapy.

A follow-up abdominal CT scan performed on November 14, 2024, showed a marked reduction of the intra-abdominal abscess (Figure 1C).

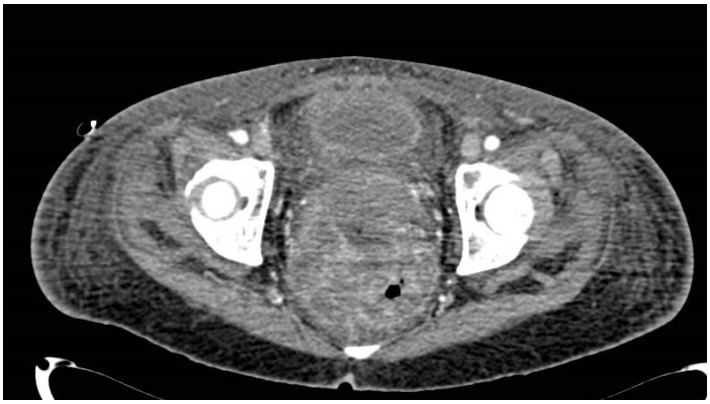

Figure 1C: Postoperative CT scan showing intra-abdominal complications, including fluid collections and signs of infection following emergency surgical intervention.

Following clinical and blood chemistry tests improvement, the patient was discharged with antibiotic therapy, home care assistance and ongoing VAC therapy.

Following a multidisciplinary re-evaluation of CT scans performed throughout the patient's clinical course, the observed radiological changes were interpreted as potentially consistent with pseudoprogression, a phenomenon well described in patients receiving immune checkpoint inhibitors and characterized by transient lesion enlargement related to immune-mediated inflammatory changes. This interpretation was supported by the absence of unequivocal radiological features of true progression, the lack of distant disease dissemination and the discordance between the observed imaging findings and the expected clinical trajectory reported in the available literature. In this context, and in alignment with the patient's informed and firmly expressed preference to avoid demolitive surgery, continuation of immune checkpoint inhibition was considered the most appropriate therapeutic strategy; therefore, treatment with dostarlimab was resumed.

However, subsequent CT scan performed after four cycles of ICI (January 21, 2025) revealed unequivocal radiological progression of the rectal mass (11×10 cm vs. 7×8 cm), with infiltration into the vaginal lumen and cervical uterus, along with worsening of the abscess. The fistulous tract persisted. The formation also exerted pressure on the distal third of the ureters and the bladder wall. The rapid volumetric increase and locally aggressive behavior observed at this stage suggested an unusual rapid pattern of disease progression (Figure 1D).

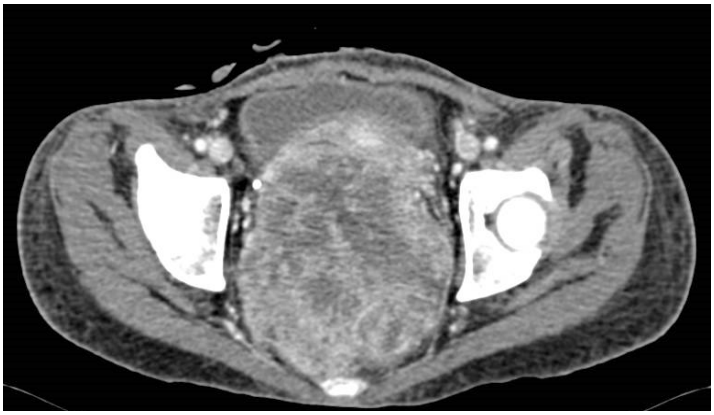

Figure 1D: Follow-up CT scan after continuation of immunotherapy revealing further enlargement of the pelvic mass with invasion of surrounding organs (vaginal lumen and uterus), worsening abscess, and persistent fistulization, consistent with hyperprogressive disease.

The case was discussed in our multidisciplinary meeting. Both radiotherapy treatment and surgical intervention were excluded at that time due to the excessive tumor extension, with a high likelihood of incomplete (R2) resection. In this setting, systemic therapy represented the only feasible therapeutic option. Given the atypical and ultimately unfavorable course observed with immune checkpoint inhibition, immunotherapy was discontinued permanently. In the clinical course of the patient, systemic chemotherapy appeared to be the only modality associated with signs of disease stabilization. In this context, and with the aim of optimizing local conditions and reassessing resectability, we proposed two cycles of mFOLFOX at a 50% dose reduction,

adjusted for UGT1A1 and DPYD polymorphisms as well as the patient's clinical status, with the intent of subsequent surgical re-evaluation.

However, only one cycle of chemotherapy was administered, as in February 2025 the patient required hospitalization due to clinical deterioration. The new CT scan showed an anterior-cutaneous fistulous tract opening at the right intergluteal fold, approximately 3 cm in length with a 3-4 mm skin discontinuity, likely communicating with a previously noted gluteal muscle fluid collection, now increased in size (48 mm vs. 40 mm), with surrounding edema. There were signs of renal distress, bilateral ureteral hyperemia and slight swelling of both kidneys. Blood tests confirmed the presence of sepsis. A new perianal drain was placed and antibiotic therapy was started based on the results blood cultures (Figure 1E).

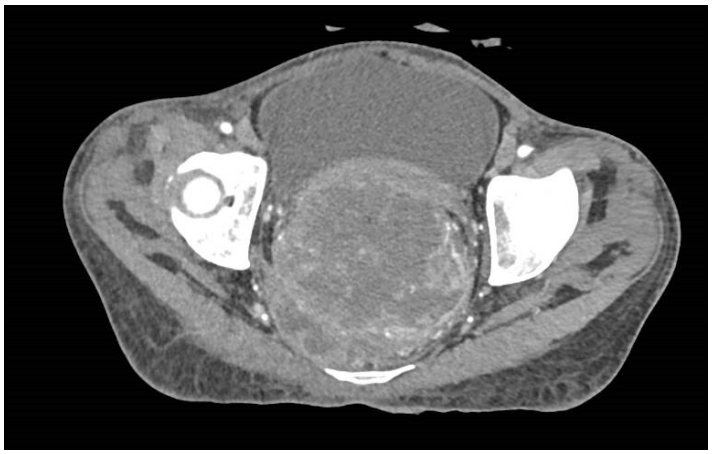

Figure 1E: Late-stage CT scan demonstrating extensive local disease progression with complex fistulous tracts, gluteal fluid collections, and signs of systemic complications including renal involvement.

Given the disease extent, the associated complications, the limited response to both chemotherapy and immunotherapy, the colorectal surgery equipe proposed a palliative surgical debridement aimed at draining the abscessed areas. However, the patient and her caregivers refused the procedure. During the following days the patient's conditions deteriorated, with progressive drowsiness and unresponsiveness. The patient died on February18th, 2025. (Figure 2).

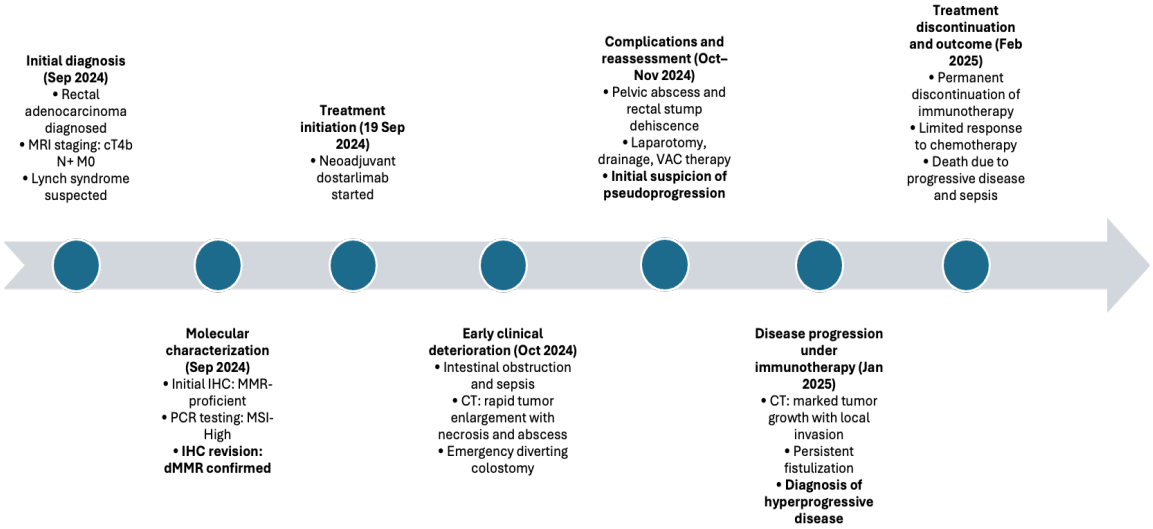

Figure 1: Case report timeline

Discussion

This case report holds significant translational relevance, as it highlights an immunotherapy response pattern that remains poorly documented in the context of newly approved treatments for rectal cancer.

The advent of immune checkpoint inhibitors (ICIs) has introduced new therapeutic challenges, not only in terms of toxicity but also with respect to the heterogeneity of tumor response patterns. Among these, hyperprogressive disease (HPD) has emerged as an unexpected phenomenon, characterized by the rapid acceleration of tumor growth following the initiation of immunotherapy [8]. However, despite its recognition in various malignancies, HPD remains poorly understood, with no established predictive biomarkers or universally accepted diagnostic criteria. Several definitions have been proposed in the literature: some define HPD as a tumor growth rate (TGR) at least twofold higher during ICI therapy compared to the pre-treatment period; others consider it as a ≥50% increase in tumor burden within a time to treatment failure (TTF) of less than two months, with a doubling of progression pace. Another widely accepted definition describes HPD as a ≥50% increase in disease burden at the first radiological assessment after therapy initiation [9]. This concept remains controversial, as most studies lack a control arm, making it difficult to determine whether disease acceleration is a direct consequence of immunotherapy. However, tumor growth rate and tumor kinetics remain the key parameters to identify this pattern. Our case fits the third definition and closely aligns with the second. Due to the lack of sufficient pre-treatment TGR data, we are unable to determine whether it meets the first criterion. The sharp increase in tumor burden shortly after the initiation of immunotherapy may raise the question of whether this represents true HPD or pseudoprogression. Pseudoprogression is characterized by initial tumor enlargement due to immune cell infiltration, followed by tumor regression [10]. Given the early radiological enlargement in contrast with the strong evidence of efficacy reported in pivotal trials, we initially suspected a pseudoprogression. This pattern is classified as atypical response and it's observed in particular in patients undergoing immunotherapy [11]. However, in our case, tumor progression did not subsequently regress, suggesting true HPD rather than a transient inflammatory response. This underscores the need for improved criteria to distinguish between HPD and pseudoprogression, as misclassification could lead to premature discontinuation of an effective therapy or inappropriate continuation of an ineffective one.

The reported incidence of HPD varies between 4% and 29% and typically manifests early during therapy [9]. While it has been described across multiple histologies, it appears to be more common in non-small cell lung cancer (NSCLC), urothelial carcinoma, and head and neck tumors [8, 12]. HPD is associated with poorer overall survival (OS) and progression-free survival (PFS), significantly reducing the likelihood of response to subsequent treatments [8, 9]. Though much remains unknown, the impact on patient outcomes has prompted research to better characterize its mechanisms and predictive factors.

The genomic landscape of HPD remains an area of active investigation. Several studies have attempted to identify specific genomic aberrations associated with this phenomenon. Among them, MDM2/4 amplifications and EGFR alterations have been the most strongly linked to HPD [12-14].

From a pathophysiological standpoint, HPD appears to be driven by modulation of a subset of immunosuppressive cells and differential antibody domain responses. The tumor microenvironment (TME) and variations in T-cell subtypes play a complex role, particularly involving senescent CD4+ T cells and M2-like epithelioid macrophages. Additionally, several studies suggest a potential role for CCR7-negative, CD45RA-negative, TIGIT-negative CD8+ lymphocytes [9]. The rapid and aggressive tumor progression observed in our patient, with lesions characterized by necrosis and abscess formation, raises the hypothesis that immune system overstimulation could paradoxically have promoted an inflammatory response favoring tumor growth rather than regression. In addition, it should be noted that our patient developed a severe infectious and septic clinical course early during treatment, a condition that may have contributed to immune dysregulation and potentially impaired the effectiveness of immune checkpoint blockade.

Several studies have reported on HPD associated with different immune checkpoint inhibitors (anti-PD1, anti-PD-L1), though none specifically involved Dostarlimab [15]. Nonetheless, Dostarlimab has been extensively used in various oncological settings, demonstrating a well-tolerated safety profile. It is a humanized IgG4 monoclonal antibody that binds PD-1 on T cells, blocking interactions with PD-L1 and PD-L2, thereby activating antitumor immune responses. It exhibits high binding affinity, comparable to other anti-PD-1 antibodies, including Nivolumab, Pembrolizumab and Cemiplimab.

In the GARNET trial, Dostarlimab was evaluated in patients with recurrent endometrial cancer who had progressed after platinum-based chemotherapy or had received ≤2 prior lines of treatment for recurrent/advanced disease. Patients received 500 mg IV Q3W for four cycles, followed by 1000 mg IV Q6W until disease progression. In an interim analysis (2022), the progression rate among dMMR patients was 39%, whereas in the MSI-H cohort, no progression was observed. Treatment-related adverse events (TRAEs) were predominantly grade 1-2. The most common grade

3 TRAEs included hematologic toxicity, diarrhea, and fatigue. treatment discontinuation occurred in 5.5% of patients, primarily due to hepatic function alterations, with no treatment-related deaths. There were no clear reports of treatment discontinuation specifically attributed to HPD [16].

In the registrational trial that led to Dostarlimab approval for locally advanced rectal cancer, the drug was administered at 500 mg every 3 weeks for 6 months (9 cycles), followed by chemoradiation therapy. Patients who had a clinical complete response after completion of either induction therapy with Dostarlimab or after chemoradiotherapy underwent nonoperative follow up. The baseline clinical and radiological characteristics of our patient were comparable to those in the registrational trial cohort, with an age range of 26-78 years, 10% female patients, 12% with ECOG PS 0, 19% with T4 tumors (including one T4b case), and 94% with nodal involvement. In the registrational study, no subgroup analyses were performed according to the underlying mismatch repair germline gene. Moreover, robust evidence supporting clinically meaningful differences in immunotherapy outcomes among the various Lynch syndrome–associated genes is currently lacking. However, the limited available gene-specific data suggest that tumors associated with germline MLH1 variants, such as in our patient, belong to the subgroup with the most favorable expected outcomes under immune checkpoint blockade. [17] Despite these similarities, the therapeutic response in our case was markedly different. In the registrational trial, 100% of patients achieved a pathological complete response (pCR), with no recurrences or disease progression after 12 months of follow-up. Clinical response was observed early, with symptom resolution in >50% of patients within 9 weeks of Dostarlimab initiation. Moreover, no grade 3 or higher toxicities were reported [3]. The absence of HPD in registrational trials does not necessarily exclude its occurrence in real-world practice. One possibility is that patient selection criteria may have favored individuals with a less aggressive disease biology.

Although larger cohorts and longer follow-up are clearly needed, currently available real-world data already describe clinical trajectories that, in selected cases, overlap with the course observed in our patient. While the registrational trial was based on a very limited sample size, evidence emerging from broader real-world experiences suggests more heterogeneous responses to neoadjuvant immune checkpoint inhibition in dMMR/MSI-H locally advanced rectal cancer, including cases of primary resistance and unfavorable outcomes.

It should in fact be considered that even tumors characterized by mismatch repair deficiency and high microsatellite instability may fail to respond to immune checkpoint inhibitors because of primary or secondary resistance mechanisms. These mechanisms can be intrinsic to the cell, such as a low or heterogeneous mutational burden, insensitivity to T cells, or aberrant oncogenic signaling pathways, including MAPK activation or WNT/β-catenin signaling, which can promote T-cell exclusion within the tumor microenvironment. Disruption of interferon-γ signaling, particularly through alterations in the JAK/STAT axis, may further impair immune-mediated cytotoxicity and reduce responsiveness to PD-1 blockade. In addition, defects in antigen presentation due to alterations in β2-microglobulin or HLA molecules may limit effective T-cell recognition despite preserved microsatellite instability.

Resistance may also be mediated by tumor cell–extrinsic factors, including insufficient tumor-infiltrating lymphocytes, dysfunction of antigen-presenting cells, or the presence of immunosuppressive populations such as tumor-associated macrophages and regulatory T cells. Furthermore, upregulation of alternative inhibitory immune checkpoints, including LAG-3, TIM-3, TIGIT, or VISTA, may contribute to adaptive immune escape [18, 19].

These observations support the need for future studies to focus on patient stratification, to identify those who derive durable benefit from immunotherapy alone and those who may instead require treatment escalation or alternative therapeutic strategies [20-22].

Conclusion

This case highlights that responses to immune checkpoint inhibitors in dMMR/MSI-H locally advanced rectal cancer is more heterogeneous than initially suggested by registrational trials. The biological and clinical complexity emerging from real-world experiences underscores the need for improved patient stratification beyond MSI/MMR status alone. Future efforts should focus on identifying predictive biomarkers of benefit and resistance, in order to tailor treatment intensity and optimize outcomes and minimize the risk of unfavorable courses.

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