RECURRENT RECTAL ADENOCARCINOMA WITH KRAS MUTATION POST-MFOLFOX6/BEVACIZUMAB REMISSION: A CASE REPORT

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ABSTRACT

Background: This case report elucidates the clinical trajectory of a 41-year-old male diagnosed with low rectal adenocarcinoma, further complicated by pulmonary metastases, harboring a KRAS mutation, and characterized by microsatellite stability.

Case Presentation: This patient demonstrated a significant and favorable response to neoadjuvant chemotherapy with a modified FOLFOX6 (mFOLFOX6) regimen in combination with bevacizumab, an anti-VEGF monoclonal

antibody. This therapeutic intervention culminated in a complete remission, meticulously confirmed through Positron Emission Tomography/Computed Tomography (PET/CT) imaging. Subsequently, the patient was transitioned to a maintenance therapy protocol involving intermittent cycles of the same regimen to consolidate the achieved remission. However, after a six-month period of maintenance therapy, the patient experienced metastatic recurrence, unequivocally identified by the emergence of Fluorodeoxyglucose-avid lesions in the lungs, mesenteric nodes, and left adrenal gland.

Biopsies of the mesenteric and adrenal lesions pathologically confirmed adenocarcinoma, exhibiting an identical KRAS mutation and microsatellite stability profile to the primary tumor, strongly indicating disease progression rather than the manifestation of a new primary malignancy.

The patient was subsequently initiated on a regimen of bevacizumab and capecitabine as salvage therapy, and the patient was radiotherapy or surgery naive which provides an opportunity to further explore alternative treatment strategies in this complex scenario.

Conclusion: This case underscores the inherent challenges in the clinical management of advanced rectal cancer, specifically highlighting the potential for acquired resistance to anti-angiogenic therapies such as bevacizumab, despite an initial robust response. Furthermore, it emphasizes the critical importance of vigilant and continuous monitoring for disease recurrence, even in patients who have achieved complete remission following first-line treatment strategies.

Keywords: colorectal cancer, Nigeria, KRAS mutation, microsatellite instability

INTRODUCTION

Colorectal cancer stands as a significant global health burden, ranking as one of the most prevalent malignancies and a leading cause of cancer-related mortality worldwide.[1] The management of advanced colorectal cancer, particularly metastatic disease, necessitates a multifaceted approach, integrating systemic chemotherapy, targeted therapies, and surgical interventions, tailored to the individual patient's disease characteristics and overall health status.[2] Approximately 20% of patients present with metastatic disease at initial diagnosis, and a substantial proportion of patients experience disease recurrence following surgical resection, typically manifesting in the liver or lungs.[3] The introduction of oxaliplatin and irinotecan into clinical practice significantly improved overall survival to nearly 24 months when combined with 5-FU.[4] First-line therapy of advanced or metastatic colorectal carcinoma usually consists of the administration of oxaliplatin or irinotecan in combination with leucovorin and 5-fluorouracil.[5] Vascular endothelial growth factor is a key factor in tumour angiogenesis, which is critical for growth of solid tumours and spread of metastases.[6] Thus, it has become a target for cancer therapy.[7]

The integration of targeted therapies, such as anti-epidermal growth factor receptor and anti-vascular endothelial growth factor monoclonal antibodies, in conjunction with conventional chemotherapy regimens, has led to significant improvements in progression-free survival and overall survival in selected patient populations.[8] However, despite these advances, a considerable proportion of patients eventually develop resistance to these therapies, underscoring the need for a deeper understanding of the underlying mechanisms

of resistance and the development of novel therapeutic strategies.[9]

Rectal cancer management requires a collaborative multidisciplinary approach, including surgeons, radiation oncologists and medical oncologists.[10] The standard of care for locally advanced rectal cancer is neoadjuvant chemoradiation followed by total mesorectal excision. Chemoradiation is often 5-FU based, but capecitabine is an acceptable alternative. The addition of oxaliplatin to fluoropyrimidine-based chemoradiation has been investigated and has not shown to improve outcomes.

KRAS mutations are frequently observed in colorectal cancer, with prevalence rates ranging from 30% to 50%, and serve as critical biomarkers for predicting response to anti-EGFR therapies. Microsatellite instability is another important molecular feature that can influence treatment decisions, particularly in the context of immunotherapy.

This case report presents a unique scenario of a patient with KRAS-mutated, microsatellite-stable rectal adenocarcinoma who initially achieved complete remission with neoadjuvant mFOLFOX6 plus bevacizumab, followed by metastatic recurrence after a period of maintenance therapy, thereby emphasising the complexities of managing advanced colorectal cancer and the potential for acquired resistance to anti-angiogenic therapies.[11] This case highlights the importance of vigilance and continuous monitoring for disease recurrence, even after achieving complete remission with first-line treatment strategies, and underscores the need for further research into the mechanisms of acquired resistance and the development of novel therapeutic strategies to overcome these challenges.

CASE PRESENTATION

A 41-year-old male with no significant past medical history presented with complaints of rectal bleeding and altered bowel habits. Colonoscopy revealed a mass in the distal rectum, which was subsequently biopsied and confirmed to be adenocarcinoma.

The patient was diagnosed with low rectal adenocarcinoma with synchronous pulmonary metastases in March 2023. Staging evaluation included a comprehensive assessment with pelvic magnetic resonance imaging to determine tumour and node stage, as well as a computed tomography of the chest, abdomen, and pelvis to rule out distant metastatic disease.[12]

Molecular testing of the tumour using PCR revealed the presence of a KRAS mutation at exons 2, 3 and 4and microsatellite stability, which has implications for treatment decisions.

MANAGEMENT

Given the extent of disease, the patient was initiated on neoadjuvant chemotherapy with mFOLFOX6 plus bevacizumab on 4th April 2023, a regimen commonly used in the treatment of advanced colorectal cancer.

After several 6 cycles of neoadjuvant chemotherapy, which spanned between 4th April 2023 and 7th October 2023, a restaging PET/CT scan demonstrated a complete metabolic response in the rectum and lungs,

indicating a complete response (as per RECIST).

Following the achievement of complete remission, the patient was transitioned to maintenance therapy with intermittent cycles of mFOLFOX6 plus bevacizumab on 13th November, 2023.

After approximately six months of maintenance therapy, he developed new symptoms, including abdominal pain and weight loss, in May 2024.

Repeat imaging revealed the emergence of new FDG-avid lesions in the lungs(multiple intensively avid lung lesions bilaterally, largest about 2.9cm in the medial left lower lobe SUVmax 10 and 2.2cm in the left upper lobe SUVmax 17), liver (multiple hepatic metastases largest measures 3.5cm x 3.2cm SUVmax 16), and left adrenal gland(measured about 7cm x 5 cm SUVmax 15), suggestive of metastatic recurrence, however, there was still no disease in the rectum.

Biopsies of the adrenal lesions confirmed adenocarcinoma with identical KRAS mutation and microsatellite stability profiles as the primary tumour.

This ruled out the possibility of a new primary malignancy and confirmed disease progression, with no disease in the rectum.

Given the progression of disease on first-line therapy, with no disease in the rectum, the patient was offered individualised treatment, thereby avoiding both extensive surgery and radiation therapy to the rectum. He was subsequently started on second-line chemotherapy with Xeloda and bevacizumab.

He is clinically stable, awaiting a repeat PET/CT scan to assess response to treatment and determine the next line of action.

Ethical approval was obtained from the Hospital's Ethics and Research Committee, and informed consent was also obtained from the patient.

DISCUSSION

The management of advanced rectal cancer represents a significant clinical challenge, requiring a multidisciplinary approach that integrates surgical resection, radiation therapy, and systemic chemotherapy.

The case presented herein illustrates the complexities of treating rectal adenocarcinoma with pulmonary metastases, especially in this context, which may suggest acquired resistance to anti-angiogenic therapies.[13]

The patient's initial favourable response to neoadjuvant mFOLFOX6 plus bevacizumab, leading to complete remission, underscores the efficacy of this treatment regimen in certain patient populations.[14]

However, the subsequent development of metastatic recurrence after 6 months of maintenance therapy highlights the potential for tumour cells to develop resistance mechanisms, ultimately leading to disease progression.[15]

The development of acquired resistance to anti-angiogenic therapies, such as

bevacizumab, is a recognised phenomenon in colorectal cancer treatment.

Several mechanisms have been proposed to explain this resistance, including upregulation of alternative angiogenic pathways, increased tumour invasiveness, and the selection of resistant tumour cell clones.[16,17]

The emergence of FDG-avid lesions in the lungs, liver, and left adrenal gland in this patient suggests the development of widespread metastatic disease despite ongoing anti-angiogenic therapy.
The fact that biopsies of the adrenal lesions confirmed adenocarcinoma with identical KRAS mutation and microsatellite stability profiles as the primary tumour further supports the notion of disease progression rather than a new primary malignancy.

The decision to initiate second-line chemotherapy with Xeloda and bevacizumab was based on the available evidence and clinical guidelines for the treatment of metastatic colorectal cancer.

Xeloda, an oral fluoropyrimidine, is commonly used in combination with other agents in the treatment of advanced colorectal cancer.

The reintroduction of bevacizumab in the second-line setting was considered due to the potential for continued benefit from anti-angiogenic therapy, despite the development of resistance to the initial regimen.[18,19]

The patient's radiotherapy and surgery naive status further influenced the treatment approach, as these modalities could be considered as potential options in the management of recurrent disease.

Angiogenesis inhibitors such as bevacizumab have shown a survival advantage when combined with chemotherapy for patients diagnosed with metastatic colorectal cancer.[20,21]

The RAS mutation status plays a critical role in determining the efficacy of anti-EGFR monoclonal antibodies (mAbs) like cetuximab and panitumumab in metastatic colorectal cancer (mCRC).[22]
The optimal strategy for combining and sequencing the available drugs in routine practice has not been established.[23]

The presence of a KRAS mutation in this patient's tumour has implications for treatment decisions, as it is associated with resistance to epidermal growth factor receptor inhibitors.[24]

The microsatellite stability status of the tumour also provides important information, as it indicates a lower likelihood of response to immune checkpoint inhibitors.

In patients with microsatellite-stable tumours, chemotherapy remains the mainstay of treatment, with targeted therapies and other novel approaches being explored in clinical trials.[25]

The case underscores the importance of vigilant monitoring for disease recurrence even after achieving complete remission with first-line treatment.

Regular imaging studies and biomarker assessments are essential for detecting early

signs of recurrence and guiding subsequent treatment decisions.

The treatment of metastatic colorectal cancer (mCRC) has evolved significantly over the past few decades, with the introduction of new chemotherapeutic agents, targeted therapies, and immunotherapies.

However, despite these advances, the development of resistance to treatment remains a major challenge, and further research is needed to identify novel strategies for overcoming this obstacle.
The identification of KRAS mutations in colorectal cancer has significant implications for treatment decisions, as these mutations are associated with resistance to anti-EGFR therapies.[26]

Therefore, patients with KRAS-mutated tumours are unlikely to benefit from treatment with cetuximab or panitumumab.[27] The continued monitoring and treatment adaptations demonstrate the dynamic nature of cancer care and the necessity for customised treatment strategies based on individual patient responses and disease characteristics.

The initial response to mFOLFOX6 plus bevacizumab, followed by recurrence, highlights the complex dynamics of targeted therapies and the potential for tumours to evolve resistance mechanisms.

The case is a valuable contribution to the understanding of treatment resistance in advanced rectal cancer.

Limitation of this case report is that it's a single case study, and as such, cannot be generalised.

CONCLUSION

This case report highlights the complexities of managing advanced rectal adenocarcinoma, particularly in the context of acquired resistance to first-line treatment. While the patient initially achieved complete remission with mFOLFOX6 plus bevacizumab, the subsequent recurrence underscores the need for continued research into novel therapeutic strategies to overcome resistance mechanisms and improve long-term outcomes. Continued medical therapy remains the mainstay of treatment for patients who progress while on treatment. The case also emphasises the importance of vigilant monitoring for disease recurrence and the role of patient-reported symptoms in guiding diagnostic workup. The identification of predictive biomarkers and the development of personalised treatment approaches are crucial for optimising outcomes in patients with advanced colorectal cancer.

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