Advancements in Lynch Syndrome Management: Applying Immunotherapy for Therapeutic Success

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Abstract

Lynch syndrome is the fourth most common cancer in the United States, with an early age of onset and poor prognosis. Here, we present a unique case of a patient with progressive colon cancer due to a late diagnosis of Lynch syndrome showing excellent response to immunotherapy. A 59-year-old male with a history of rectal cancer 30 years ago came to the hospital due to a fever and further found a large necrotic colon mass. Biopsy was positive for colorectal cancer; however, due to the size of the tumor, the patient was deemed not a surgical candidate and offered hospice with palliative chemotherapy. Based on further workup, the patient was diagnosed with Lynch syndrome, with colon cancer determined to be responsive to Immunotherapy. He was started on JEMPERLI (Dosterlimab-gxly), and after three cycles of therapy, imaging and PET scan were repeated, showing decreased activity and extent of the tumor—a tremendous success.

Keywords

Lynch Syndrome, Colon Cancer, Genetics, Immunotherapy, Dostarlimab

1. Introduction

Lynch syndrome is the fourth most common cancer in the United States, with an onset at the age of 45 to 60 compared to sporadic colorectal cancer, most commonly seen at 69 years old [1]. According to the CDC data, people with Lynch syndrome are susceptible to getting not only colorectal cancer but other cancers at a younger age (before 50 years old) as well. The most commonly affected organs are the Uterus (endometrial cancer), Stomach, Liver, Kidney, Brain, and Skin.
The disease’s mechanism involves inherited or less commonly sporadic mutations in DNA mismatch repair genes. These mutations lead to a broken mechanism of fixing DNA mistakes during replication, resulting in “microsatellite instability” and tumor formation [2]. Usually, such genes (MLH1, MSH2, MSH6, PMS2, and EPCAM) are working to protect from cancer; however, in the case of mutation, the protective mechanism is absent, leading to different malignancies combined as Lynch syndrome.

Lynch syndrome causes about 4300 colorectal cancers and 1,800 uterine (endometrial) cancers per year [3] [4]. While there is no cure for Lynch syndrome, sometimes chemo and radiation therapy followed by surgery with almost complete resection of an organ can be performed to decrease tumor burden; however, in most cases, it is done as a palliative treatment. Here, we present a case of recurrent, progressive cancer in a patient with a late diagnosis of Lynch syndrome and an excellent response to immunotherapy with a checkpoint inhibitor.

2. Case Description

A 59-year-old male with a history of rectal cancer 30 years ago, at that time requiring neoadjuvant concurrent radiation and chemotherapy followed resection and adjuvant chemotherapy/colostomy placement, came to the hospital due to fever. While a routine laboratory blood and urine workup was suspicious for urinary tract infection, imaging unexpectedly showed irregular rectal wall thickening and a large necrotic colon mass approximately 9.6 × 7 × 7.5 cm in size, growing to the front, perforating the bladder, and growing up, obstructing the ureter, causing hydronephrosis (Figure 1). The biopsy performed by interventional radiology showed positive for adenocarcinoma and high likelihood of his rectal cancer recurrence. Positron emission tomography (PET scan) was ordered, which confirmed malignant fistulation of the rectal mass into the adjacent bowels, bladder, and pelvic sidewalls with erosion into the sacrum (Figure 2). The patient was not a surgical candidate due to the visualized high tumor burden. Patient had significant decline in his health during the work up and was offered hospice, which he agreed to proceed with since he was considered not a chemotherapy candidate. Patient was also homeless which further complicated his treatment process.

In the meantime, molecular testing on biopsied tissue with next generation sequencing was sent and was positive for microsatellite instability and High TMB. Immunohistochemistry also had confirmed mismatch repair protein loss. Further evaluation with genetic testing was positive for a frame shift mutation in the MSH2 gene at the following coding location of the DNA – c.1972_1973ins (p. Glu658fs) in a heterozygous state. Based on available data from genetic databases and computational predictors, the variant was interpreted as pathogenic, leading to a loss of expression of the MSH2 gene, consistent with Lynch syndrome. On further history taking, the patient had a positive family history of colon cancer in his grandparents, further confirming the diagnosis. Based on the results, the
Figure 1. Large necrotic mass in rectum with malignant fistulation into adjacent organs (the white circle shows the extent of rectal cancer).

Figure 2. PET scan before therapy with Dostarlimab showing malignant fistulation of the rectal mass into the adjacent bowels, bladder, and pelvic sidewalls with erosion into the sacrum (white circle).

tumor was determined to be responsive to immune checkpoint inhibitor targeting the programmed cell death-1 receptor [5]. Due to the potential colon cancer response immunotherapy, the patient was offered to start an active treatment with JEMPERLI (Dostarlimab-gxly). After three cycles of therapy, an imaging and PET scan were repeated, which showed decreased activity and extent of the tumor—a tremendous success (Figure 3). He also has clinically improved with significant improvement in his symptoms from rectal cancer and overall performance status.

3. Discussion

Lynch syndrome is the most common cause of inherited colorectal cancer (CRC), responsible for 2% - 4% of newly diagnosed CRC cases [6]. It is transmitted in an autosomal dominant pattern and caused by germline mutations in the following mismatch repair genes: MLH1, MSH2, MSH6, and PMS2 or in the epithelial cell adhesion molecule gene (EpCAM) [7] [8].

While Amsterdam II criteria (based on the patient or family history of cancer) and revised Bethesda guidelines (based on patient, family history, and histologic tumor findings) were created to facilitate the diagnosis of Lynch syndrome, it is
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Figure 3. PET scan after 3 cycles of Dostarlimab shows decreased colon cancer activity and the extent of the tumor (the red circle shows a significantly reduced burden of rectal cancer in comparison with the red circle in Figure 2).

often missed due to the rare nature of the disease and, as a result, low clinical suspicion. However, recently, the guidelines changed and now recommend universal testing of all patients diagnosed with colorectal cancer for microsatellite instability [1] [6] [7] [8] [9].

While our patient was diagnosed with rectal cancer at the early age of 30 years old, no further screening testing for microsatellite instability was performed at that time. As a result, he missed the appropriate surveillance program and presented much later with progressive rectal cancer mimicking symptoms of UTI. After joint consultations with several specialists regarding advanced biopsy-proven rectal cancer, the patient was offered palliative chemotherapy initially [10], however, due to his significant decline in health during the process, he was placed in hospice. Once he was confirmed with lynch syndrome, hospice was discontinued, and immunotherapy was started.

Based on current scientific and diagnostic standards, patients are advised to undergo genetic counseling and testing after positive screening for microsatellite instability with loss of mismatch protein. The patient and his family were offered genetic counseling, where the built family pedigree clearly showed cancer in direct family relatives, confirming the inheritance component of cancer development. Further genetic testing was positive for a germline pathogenetic variant in the MSH2 gene in the heterozygous state. Still, since the disease is inherited in an autosomal dominant manner, only one allele is required to cause the phenotype, which led to the diagnosis of Lynch syndrome.

Based on the guidelines and according to the results of the patient’s immunohistochemical testing, the tumor was determined to be responding to anti-programmed death 1 (PD-1) monoclonal antibody. It’s been shown that tumors with microsatellite instability have increased tumor-infiltrating lymphocytes and enhanced expression of programmed cell death 1 (PD-1) receptors [11]. By binding the PD-1 ligands on cancer cells and the PD-1 receptor on
T-cells, tumor cells can inhibit cytokine secretion and T-cell proliferation, which leads to unrecognized tumor proliferation. However, by blocking the PD-1 receptor on T-cells, Immunotherapy enhances T-cell ability to recognize and attack tumor cells, decreasing the tumor size and preventing further tumor progression [12]. Based on the findings of a non-randomized controlled trial by Thierry et al., JEMPERLI (Dostarlimab-gxyl) was a well-tolerated treatment option with rapid, robust, and durable antitumor activity in patients with microsatellite instability tumors [11]. As a result, our patient was started on new immunotherapy with JEMPERLI (Dostarlimab-gxyl).

After initiating the cancer therapy with JEMPERLI (Dostarlimab-gxyl), the current guidelines recommend checking the response to treatment after 2 - 3 cycles of immunotherapy and then performing scans every 3 - 6 months for the first 2 years of therapy, followed by scans every 6 months for 5 years and then as needed in case patients develop symptoms. The goal is to continue immunotherapy for 2 years and then discontinue if he achieves a complete response. Imaging evaluation in our patient showed excellent results: both the tumor size and activity have decreased, which are the main criteria for assessing therapy effectiveness. No significant adverse reactions to medication were observed so far.

For surveillance in patients with colorectal cancer with microsatellite instability, it's recommended to perform genetic counseling first and then colectomy with ileorectal anastomosis followed by colonoscopy every year, prophylactic hysterectomy, and bilateral salpingo-oophorectomy when childbearing is complete, and urinalysis with urine cytology every year from the age of 30 - 35 years [6]. In our patient, appropriate screening for him and his family was offered after extensive genetic counseling.

While immune checkpoint inhibitors are a standard treatment for patients with metastatic colorectal cancer and deficient mismatch repair, PD-1-blocking monoclonal antibodies are not yet commonly used [1]. Our case shows the power of genetic and immunohistochemical testing and the fantastic results of immunotherapy. Even though it is considered metastatic colorectal cancer in Lynch syndrome not a curative disease, with the availability of immunotherapy, the cure may not be too far from way in this patient population. Therefore, this case highlights the power of immunotherapy in Lynch syndrome associated colorectal cancer and awareness of powerful treatment available for Lynch syndrome associated cancers in the GI community.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References


