Advanced Research in Gastroenterology & Hepatology
ISSN: 2472-6400

Juniper Publishers
key to the Researchers

Case Report
Volume 20 Issue 3 - March 2024
DOI: 10.19080/ARGH.2024.20.556039

Adv Res Gastroentero Hepatol

A Remarkable Response to Neoadjuvant Immunotherapy in Lynch Syndrome

Aneri Patel[1,3]*, Alex Chiang[2] and Rashmi Verma[3]

[1,3]*University of California Davis School of Medicine, USA*

[3]*Department of Hematology and Oncology at University of California North state, USA*

[2]*California North state University College of Medicine, USA*

Submission: February 19, 2024; **Published:** March 01, 2024

***Corresponding author:** Aneri Patel, University of California Davis School of Medicine, USA

Abstract

We present the case of a 69 year old male with history of duodenal carcinoma who was diagnosed with Lynch Syndrome. Initially, the patient was placed on adjuvant chemotherapy of FOLFOX (leucovorin calcium, folinic acid, fluorouracil, and oxaliplatin) for 6 cycles. Due to continued tumor growth refractory to adjuvant chemotherapy, the initial chemotherapy regime was discontinued and subsequently switched to neoadjuvant immunotherapy of Pembrolizumab for 4 cycles. The patient's duodenal mass subsequently showed remarkable size reduction over 3 months in response to the Pembrolizumab. While the initial goal was only to reduce tumor size and burden, the effectiveness of the therapy also led to successful resection in a case that would have otherwise been considered non-operable in the past. The patient is currently in remission and living without any therapeutic or surgical complications. There is limited literature regarding neoadjuvant immunotherapy in the setting of Lynch syndrome, making this patient's responsiveness to therapy a unique and promising case.

Keywords: Neoadjuvant Immunotherapy; Lynch syndrome; folinic acid; fluorouracil; leucovorin calcium; surgical complications; Pembrolizumab

Abbreviations: HNPCC: Hereditary Non Polyposis Colorectal Cancer; CRC: Colorectal Cancer; MCRC: Metastatic Colorectal Carcinoma; DMMR: Deficient Mismatch Repair; MSI-H: Microsatellite Instability-High

Case Report

We present the case of a 69 year old male with history of duodenal carcinoma who was diagnosed with Lynch Syndrome. The patient had a previous history of benign colon polyps, and had a second degree relative with cancer. The patient came to the gastroenterology department with a case of iron deficiency anemia. An esophagogastroduodenoscopy revealed a circumferential duodenal mass and surgical pathology showed fragments of tubulovillous adenoma with high grade dysplasia and a friable mass in the second and third portion of the duodenum–both concerning malignancy. Following staging, the patient was placed on adjuvant chemotherapy of FOLFOX (folinic acid, fluorouracil, and oxaliplatin) for 6 cycles. There was a modest reduction in tumor size from 114mm to 58mm, however, there was tumor abutment to the superior mesenteric vein and artery, and unchanged lymph nodes, so further shrinkage was required prior to surgical resection. In addition, the patient's genetic testing came back positive for MSH6 mutation, consistent with Lynch syndrome. The patient was then started on neoadjuvant immunotherapy Pembrolizumab for 3 cycles. Over 3 months, there was substantial size reduction in response to the Pembrolizumab. After two more cycles, the patient became a candidate for a Whipple procedure (as there was involvement of the uncinate head of pancreas). Post Whipple, the pancreas and duodenal scans indicated that there is no residual carcinoma, and all 45 lymph nodes are negative for cancer, indicating a complete treatment response. Patient's CT-DNA was tested by Natera testing every 3 months, and currently it is still negative. Our patient showed initial improvement in the size of the duodenal tumor size through FOLFOX. However, as the patient was found to have an aggressive duodenal tumor, unchanged lymph nodes and Lynch Syndrome, a decision to use Pembrolizumab was made, which demonstrated an impressive reduction in the tumor burden. While the initial goal was only to reduce tumor size and burden, the effectiveness of the therapy also led to successful resection in a case that would have otherwise been considered non-operable in the past. The patient is currently in remission and living without any therapeutic or surgical complications. There is limited literature regarding neoadjuvant immunotherapy in the setting of Lynch syndrome to potentially manage the cancer growth, making this patient's complete responsiveness to therapy a unique and promising case.

Background

Lynch syndrome is an autosomal dominant inherited syndrome, also called hereditary non polyposis colorectal cancer (HNPCC), and is the most common cause of inherited colorectal cancer (CRC); lynch syndrome confers an increased risk of endometrial cancer and several other malignancies, including cancers of the ovary, stomach, and genitourinary system. Most commonly, patients and families with a germline mutation in one of the DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2) or the EPCAM gene develop Lynch Syndrome [1,2]. In our case, the patient had a mutation of the MSH6 (MutS homolog 6), which is located on chromosome [3].

Introduction

A 69-year-old male with a previous history of benign colon polyps, a second degree relative with cancer presented with iron deficiency anemia to the gastroenterology department. An esophagogastroduodenoscopy revealed a circumferential duodenal mass. Surgical pathology showed fragments of tubulovillous adenoma with high grade dysplasia and a friable mass in the second and third portion of the duodenum– both concerning for malignancy. Additionally, pathology was notable for duodenal mucosa with focal acute duodenitis. Examination of the mass showed neoplastic cells arranged as papillary structures, and sometimes a villous pattern with necrosis and ulceration. Present with these neoplastic cells is an invasion with a desmoplastic reaction. Additionally, there was circumferential wall thickening of the D3 duodenum beginning right below the ampulla was also worrisome for malignancy. The team was suspicious for Lynch syndrome, given that patient had multiple duodenal masses concerning for malignancy and a strong family history. The initial immunohistochemical stains and antibody testing came back negative for MLH1, PMS2, MSH2, MSH6 (95% test sensitivity), however, given high clinical suspicion, and one of the patient's half-brothers were positive for Lynch syndrome, the patient was referred to genetic counseling. Given the duodenal cancer, the next steps for the patient included a trial of neoadjuvant chemotherapy, followed by surgical resection of the tumor. The chemotherapy included a regimen of 6 cycles of FOLFOX, but dose reduction to 5-fluorouracil (5-FU) had to be made as the patient had elevated transaminases (AST=117 and ALT=119). The patient tolerated the first 3 cycles of FOLFOX well, and the patient's liver function tests normalized after the 4th cycle of FOLFOX (AST =27 and ALT =37). Patient reported significant abdominal pain, constipation and insomnia. After 6 cycles of FOLFOX, there was an interval decrease in size and thickening of the duodenal wall, consistent with duodenal cancer. There were also unchanged enlarged lymph nodes adjacent to the duodenal mass. After collaborative efforts from the surgical oncology team, the team came to a decision for the patient to try immunotherapy to further shrink the tumor and reduce its burden before surgical resection.

In the upcoming months, the patient's genetic test was positive for MSH6 mutation, indicating Lynch Syndrome. For the patient, the immunotherapy regimen consisted of 3 cycles of Pembrolizumab. Patient noted that Pembrolizumab was easier to tolerate than his prior chemotherapy, and did not present with any GI symptoms including abdominal pain, diarrhea, constipation, nausea, but had mild neuropathy. The repeat scans post 3 cycles of Pembrolizumab indicate a reduction in size of the duodenal mass from, from 114mm to 58mm after 3 cycles of Pembrolizumab, indicated by (Figure 1 & 2). An additional 2 cycles of Pembrolizumab was indicated and added an IO agent due to MSH6 status. After the two additional cycles, the patient was considered for a Whipple procedure. Whipple procedure was indicated due to the tumor abutment to SMV and unicate head of pancreas involvement. During the Whipple surgery, The ampulla contained a visible tumor, and the mucosa around the ampulla was nodular, edematous, and red. The tumor extended from the ampullary region into the duodenum and measured 2.5 cm x 1.5 cm x 1 cm. The remaining duodenal mucosa was remarkable for papillary tumor structures at the proximal duodenal region. In addition, there was a region of duodenal mucosa proximal to the ampulla which feels nodular under the mucosa measuring 2.5 cm x 2 cm. The lymph nodes in the IVC, gallbladder, hepatic artery, omentum were negative for carcinoma. The pancreas and duodenal scans indicated that there are no residual carcinoma and all 45 lymph nodes are negative for cancer, indicating a complete treatment response. Patient's Whipple surgery was successful, and the patient had no nausea, emesis and was eating well 18 days post-surgery, and was nearly off the pain medications. Patient's CT-DNA was tested by Natera testing every 3 months, and currently it is still negative.

Discussion

The risk assessment and treatment are two very important aspects for the treatment of Lynch syndrome. Current guidelines for the management include colonoscopy beginning at age 20 to 25 repeating every one to two years; or two to five years before the earliest colorectal cancer if diagnosed before age 25 years; colectomy can be performed if colon cancer is diagnosed or if an advanced adenoma is found that cannot be otherwise removed; Hysterectomy with Salpingo-Oophorectomy after childbearing is completed for women; Endometrium (Uterus) and Ovaries in females including pelvic exam, transvaginal ultrasound, endometrial aspiration and/or CA-125 can be considered on an individual basis. The efficacy of this regimen remains uncertain. As for treatment, there has been a recent shift, which includes adding immunotherapy for more advanced cases. Recently, the anti-programmed death-1 (PD-1) antibody pembrolizumab was shown to produce significantly longer progression-free survival with fewer adverse events compared with chemotherapy as first-line treatment of metastatic colorectal carcinoma (mCRC) with deficient mismatch repair (dMMR). Therefore, single-agent pembrolizumab represents a new standard of care for dMMR, mCRCs including patients with Lynch syndrome and the more common sporadic cases [1,4]. Pembrolizumab has been established as the standard of care for patients with colorectal

How to cite this article: Aneri P, Alex C, Rashmi V. A Remarkable Response to Neoadjuvant Immunotherapy in Lynch Syndrome. Adv Res Gastroentero Hepatol, 2024; 20(3): 556039. DOI: 10.19080/ARGH.2024.20.556039

carcinoma (CRC), and its use has also been explored in the neoadjuvant setting. A recent study examined three cases of locally advanced rectal cancer where traditional treatment options such as chemotherapy, chemoradiation, and surgery were not feasible. The patients were treated with neoadjuvant immunotherapy-based systemic treatment, using pembrolizumab, nivolumab, and ipilimumab. There was a significant response in each patients' tumors following neoadjuvant immunotherapy-based treatment. The use of Pembrolizumab suggests that single-agent and combined-modality neoadjuvant immunotherapy appear to be safe and effective treatment options for patients with dMMR and locally advanced rectal cancer. 3 Additionally, In a phase 3, open-label trial, 307 patients with metastatic MSI-H–dMMR advanced colorectal cancer, it was shown that Pembrolizumab has led to significantly longer progression-free survival than chemotherapy when received as first-line therapy for MSI-H–dMMR metastatic colorectal cancer, with fewer treatment-related adverse events [5].

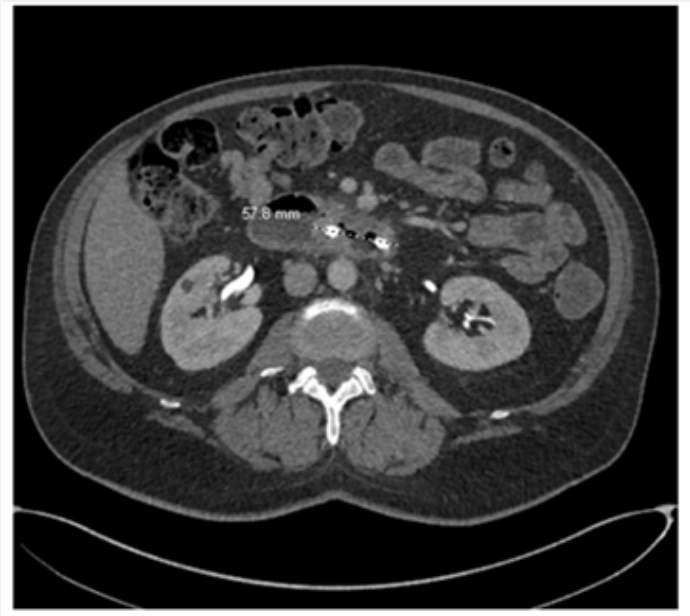

Figure 1: CT after FOLFOX, before Pembrolizumab

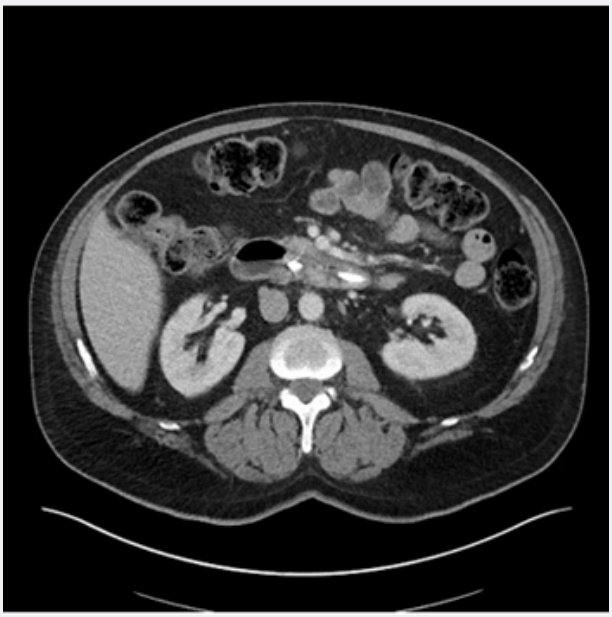

Figure 2: CT after using Pembrolizumab.

How to cite this article: Aneri P, Alex C, Rashmi V. A Remarkable Response to Neoadjuvant Immunotherapy in Lynch Syndrome. Adv Res Gastroentero Hepatol, 2024; 20(3): 556039. DOI: 10.19080/ARGH.2024.20.556039

Lastly, Pembrolizumab, is versatile and has been used to treat melanoma, non-small-cell-lung cancer and for many other cancers including metastatic colorectal cancer and microsatellite instability-high (MSI-H) or dMMR CRC [6]. The KEYNOTE-177 trial demonstrated that therapy with single-agent pembrolizumab improved progression-free survival by 8 months compared with FOLFOX or FOLFIRI and with or without EGFR inhibition. At this time, targeted therapy should only be used in patients with unresectable metastatic disease [7]. Our patient showed some initial improvement in the size of the duodenal tumor size through FOLFOX. However, as the patient was found to have Lynch Syndrome with MSI-H, a decision to use Pembrolizumab was made, which demonstrated an impressive reduction in the tumor burden. This highlights that in Lynch syndrome, and other conditions with MSI (microsatellite instability), immunotherapy response may be effective even neoadjuvant setting. NCCN guidelines recommend pembrolizumab and nivolumab for treating patients with advanced or recurrent microsatellite instability-high (MSI-H)/ mismatch repair-deficient (dMMR) EC. While immunotherapy such as pembrolizumab are not currently approved by the NCCA in either the neoadjuvant setting or in stages 1-3 of cancer, this case highlights their potential effectiveness in not only remission but overall prognostic value.

References

1. Senechal B, Elain G, Jeziorski E, Grondin V, Patey M (2007) Expansion of regulatory T cells in patients with Langerhans cell histiocytosis. PLoS Med 4(8): e253.
2. Histiocytosis syndromes in children (1987) Writing Group of the Histiocyte Society. Lancet 1(8526): 208-209.
3. Emile JF, Abla O, Fraitag S, Horne A, Haroche J (2016) Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 127(22): 2672-2681.
4. Desrame J, Béchade D, Defuentes G, Goasdoue P, Raynaud JJ (2005) Adult Langerhansian histiocytosis with sclerosing cholangitis and cerebellar atrophy [Langerhans cell histiocytosis in an adult patient associated with sclerosing cholangitis and cerebellar atrophy]. Gastroenterol Clin Biol 29(3): 300-303.
5. Baumgartner I, Von Hochstetter A, Baumert B, Luetolf U, Follath F (1997) Langerhans'-cell histiocytosis in adults. Med Pediatr Oncol 28(1): 9-14.
6. Willman CL (1994) Detection of clonal histiocytes in Langerhans cell histiocytosis: biology and clinical significance. Br J Cancer Suppl 23: S29-33.
7. Favara BE (2001) Langerhans cell histiocytosis: an identity crisis. Med Pe diatr Oncol 37(6): 545.
8. Filipovich A, McClain K, Grom A (2010) Histiocytic disorders: recent insights into pathophysiology and practical guidelines. Biol Blood Marrow Transplant16(1 Suppl): S82-S89.
9. Jaffe R (2004) Liver involvement in the histiocytic disorders of childhood. Pediatr Dev Pathol 7(3): 214-225.
10. Krishnan A, Ramakrishnan R, Venkataraman J (2012) Langerhans cell histiocytosis and choledocholithiasis: a causal relationship or coincidence? Gastroenterol Hepatol 8(11): 766-767.

DOI: 10.19080/ARGH.2024.20.556039

How to cite this article: Aneri P, Alex C, Rashmi V. A Remarkable Response to Neoadjuvant Immunotherapy in Lynch Syndrome. Adv Res Gastroentero Hepatol, 2024; 20(3): 556039. DOI: 10.19080/ARGH.2024.20.556039