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Review Article

Cohort Study of Immunotherapy in Patients with Colorectal Cancer and DNA Mismatch Repair Defects

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1. Abstract

Colorectal cancer (CRC) is the second leading cause of cancer related deaths after lung cancer and it is the third most commonly diagnosed malignancy worldwide after the lung and the breast. Immunotherapeutic agents such as checkpoint inhibitors had a FDA approval, this therapeutic approach for patients with CRC is still under development and there are more studies ongoing using checkpoint inhibitors in phase II and phase III evaluating the efficacy of these agents in patients with deficient mismatch repair (d MMR). In 15% of the CRCs there are defective DNA mismatch repair systems (MMR) caused by inactivation of mutL homologue 1 (*MLH1*), *MLH3*, mutS homologue 2 (*MSH2*), *MSH3*, *MSH6,* or PMS1 homologue 2 (*PMS2*). This may occur through inherited or sporadic mutations, or through epigenetic silencing. These dominant genomic features give rise to hyper mutations and microsatellite instability (MSI) In this study we used checkpoint inhibitors in 3 patients, (2 colon and 1 rectal cancer), one of them with metastatic stage as palliative treatment, 1 as neo adjuvant before liver metastasis resection then as adjuvant and the 3rd one as neo adjuvant after chemo radiotherapy for rectal cancer, all of the 3patients showed dramatic response.

2. Keywords: Colorectal cancer (CRC); Immunotherapy; Microsatellite instability (MSI); Mismatch repair deficient (dMMR)

3. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer related deaths after the lung cancer and it is the third most commonly diagnosed malignancy worldwide after the lung and the breast. Despite significant advances in the standard of care therapies, the 5-year survival rate for patients diagnosed with metastatic CRC remains very poor at approximately 12% [1]. In recent years, major advances had been made in the immunotherapy in many cancers as melanoma non-small cell lung cancer and renal cell carcinoma, and many of the immunotherapeutic agents such as checkpoint inhibitors had an FDA approval, this therapeutic approach for patients with CRC is still under development and there are many immune therapies currently undergoing clinical investigations [2-5]. In 15% of patients with CRCs, there have been defective DNA ismatch repair systems (MMR) caused by inactivation of mutL homologue 1 (*MLH1*), *MLH3*, mutS homologue 2 (*MSH2*), *MSH3*, *MSH6,* or PMS1 homologue 2 (*PMS2*). This may occur through inherited or sporadic mutations, or through epigenetic silencing. These dominant genomic features give rise to hyper mutations and Microsatellite Instability (MSI) [6]. In the available studies, immunotherapy had been used in metastatic MSI-H patients with CRC as the 2nd and 3rd

lines. In this study, we use immunotherapy in patients with CRC at different scenarios; neo adjuvant, metastatic and adjuvant therapy.

4. Material and Method

A cohort of dMMR colorectal cancer patients at different stages received immunotherapy and all of them had a very good outcome. One in a metastatic disease, one as neo adjuvant in rectal cancer and one in the liver metastasis before resection.

5. Case Number (1)

A 59-year-old lady diagnosed with stage III C colon cancer (T3N2M0), moderately differentiated adenocarcinoma, underwent right hemicolectomy on April, 2017.She received 12 cycles FOLFOX6 (5Flurouracil, Leucovorin and oxaliplatin) as adjuvant chemotherapy, completed on the 8th of November, 2017. Three months after she finished the adjuvant treatment, she presented with right side abdominal pain, found to have a right iliac fosse mass. Biopsy showed necrotic tissue with a tiny viable fragment showing adenocarcinoma. Loss of nuclear expression of MLH1 and PMS2.PET CT done on the 5th of March, 2018; FDG-avid extensive right ileocecal local recurrence with peritoneal masses and some retroperitoneal lymph node metastases (**Figure 1**). The RAS status not known was started on FOLFIRI (5Flurouracil, Leucovorin and Irinotecan) +bevacizumab as the 2nd line chemotherapy, received 7 cycles with severe side effects, fatigue nausea vomiting and diarrhea, admitted twice in the hospital. Initially, she had some drop-in tumor markers but later on started to rise again. Being MMR deficient, she was started on pembrolizumab 200MG intravenously every 3 weeks, tumor markers (CEA,CA19.9) started to drop but the patient continued to have severe pain in the right iliac fossa and the right lower limb. Four months later, radiotherapy was given to the right iliac fossa mass. Patient had significant improvement, the analgesia was gradually stopped, markers CEA, CA19.9) dropped to normal levels (**Figure 2**) and the mass in right iliac fossa disappeared by 6 months after the start of the treatment (**Figure 3**).

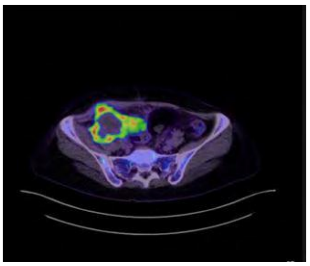

Figure 1: Case number 1, A 59 y female with colon ca, PET (Positron Emission tomography) scan for the, before start of treatment.

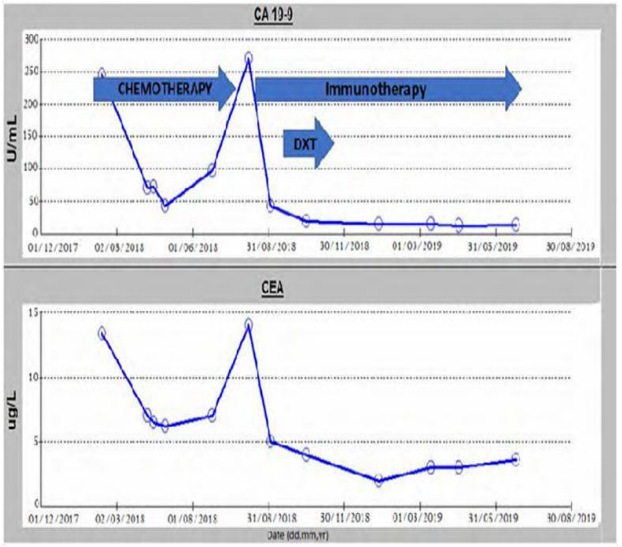

Figure 2: For the case number 1, A 59 y female with colon ca, tumor markers (CA19, 9 and CEA) level during the course of treatment.

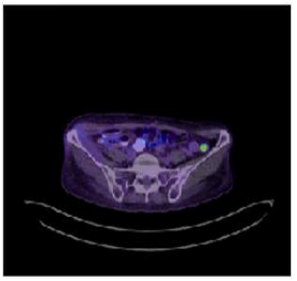

Figure 3: Case number 1, A 59 y female with colon ca, PET scan image after the 6months immunotherapy.

6. Case Number (2)

A 60 old lady had history of an Immune Thrombocytopenic Purpura (ITP) episode in 2017 which recovered spontaneously, 1 after that the patient was admitted to the hospital for low hemoglobin (5.3 gm/dl). CAT (Computerized Axial Tomography) Scan revealed a mass lesion involving the ascending colon with another long segment thickening involving the hepatic flexure and a large hypo-vascular lesion involving the left lobe with tiny satellite lesions and a few tiny similar lesions in the right lobe with adjacent enlarged necrotic lymph nodes. The features are suggestive of ascending colon neo plastic mass lesion with likely metastatic lesions of the liver. Upper & lower endoscopy show a mass in the ascending colon, a biopsy was taken & proved cancer.

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Right colonic tumor biopsies showed moderately differentiated adenocarcinoma. She underwent laparoscopic right hemicolectomy, histopathology showed moderately differentiated adenocarcinoma and the number of lymph nodes involved were 2 (2/23). Pathologic staging: pT3 N1B.MISMATCH repair protein: MSH2: loss of nuclear expression, MSH6: loss of nuclear expression, MLHI: Intact nuclear expression, PMS2: Intact nuclear expression. She received 3 cycles of chemotherapy CAPOX (Capecitabine + Oxaliplatin) with poor tolerance, admitted twice to the hospital due to adverse effects and the tumor markers (CEA, CA19.9) kept on increasing. She was started on pembrolizumab 200 mg iv every 3 weeks, received 5 cycles and tolerated very well, she had a dramatic response evidenced by both the tumor markers (**Figure 4**) and the imaging by PET scan (**Figure 5**). On May 2019, the patient underwent open left hepatectomy (with resection of the middle hepatic vein) + non-anatomical resection of small lesions in segment VIII and segment VI of the liver. The 2 grossly identified nodules are composed predominantly of mucin with scattered inflammatory cells. No viable tumor cells are identified, indicating complete response (**Figure 6**). Both lesions are completely excised. Background liver displays patchy areas of chronic inflammation. Segment VIII: Cavernous hemangioma, measuring 8 x 7 mm in the plane of section. Excision appears complete. Segment VI, benign liver parenchyma (**Figure 6**). The patient already started on adjuvant treatment withpembrolizumab for 6 months.

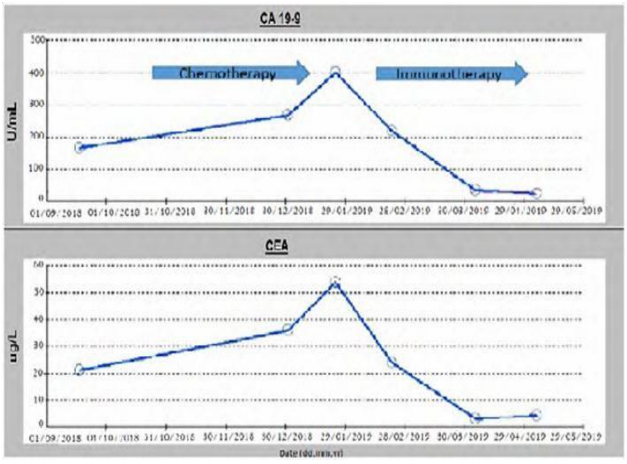

Figure 4: For the case number 2; A 60 y female with colon ca Tumor markers (CA 19, 9 and CEA) during the course of treatment.

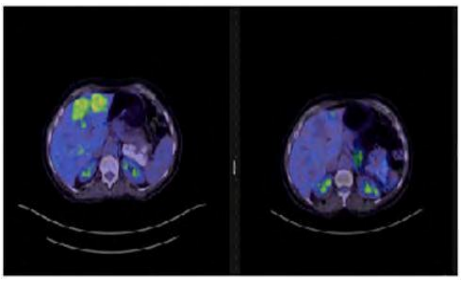

Figure 5: A 60 yrs female with colon cancer, PET Scan for case number 2; before and after the immunotherapy.

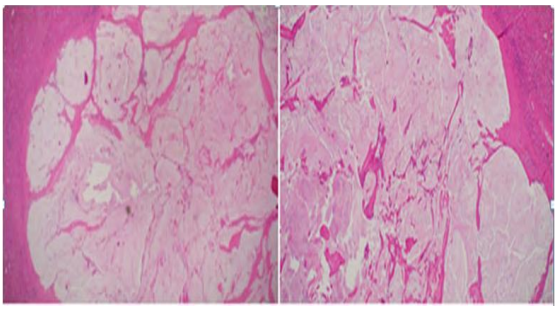

Figure 6: A 60 yrs female with colon ca, Postoperative pathology for case number 2; Mucinous nodule representing post immunotherapy changes. No residual metastatic malignancy is seen (H and E x 2).

7. Case Number (3)

A 48 years old female, known case of Lynch Syndrome, diagnosed with Colon cancer in 2016, stage II, status post right hemicolectomy, no adjuvant chemotherapy given. On 2017, she developed a recto sigmoid mass, pathology; moderately differentiated adenocarcinoma. KRAS mutant BRAF wild, Immune Histo Chemistry (IHC) for MMR revealed MLH1: loss of nuclear expression, MSH2:INTACT nuclear expression, MSH6: intact nuclear expression, PMS2: loss of nuclear expression, IHC interpretation: loss of nuclear expression of MLH1 and PMS2: testing for methylation of the MLH1 promoter and/or mutation of BRAF is indicated (the presence of a BRAF V600E mutation and/or MLH1 methylation suggests that the tumor is sporadic and germ line evaluation is probably not indicated; absence of both MLH1 methylation and of BRAF V600E mutation suggests the possibility of Lynch syndrome, and sequencing and/or large deletion/duplication testing of germ line MLH1 may be indicated). She received neo adjuvant chemo radiation, but there was still residual tumor after chemo radiotherapy (**Figure 7A**) (**Figure 7B**). She also received 2 cycles of immunotherapy, (Nivolumab) MRI showed more response (**Figure 7C**) then underwent total proctocolectomy and end ileostomy on the 25th of February, 2018. The postoperative pathology showed complete pathological remission as in (**Figure 8**).

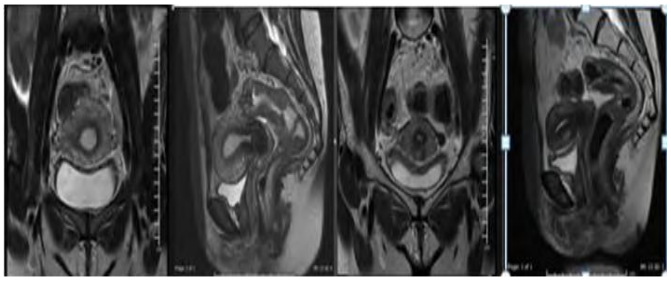

Figure 7A&B: Case number 3, 48 yrs female Ca rectum MRI before treatment (coronal and axial Figure7B. Case number 3,48 yrs female Ca rectum MRI after chemo radiotherapy treatment (coronal and axial).

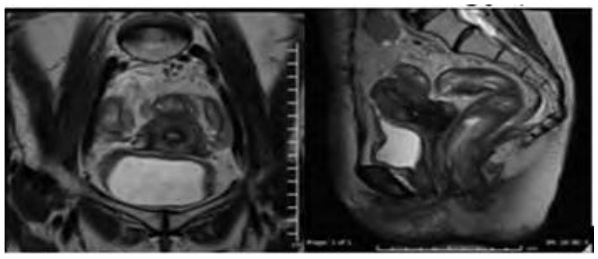

Figure 7C: Case number 3, 48 yrs female Ca rectum MRI after immunotherapy (coronal and axial).

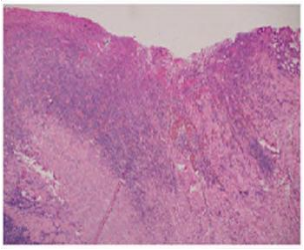

Figure 8: Case number 3, 48 yrs female Ca rectum postoperative pathology; Surface ulceration with underlying dense inflammation and fibrosis, representing post immunotherapy changes, no malignant cell seen (H and E x 4)

8. Discussion

CRC are divided into subsets based on the tumor's molecular profile which provides important predictive and prognostic information [7]. Microsatellites are short tandem DNA repeats and MSI defined as a change in the microsatellite region within the tumor cells compared to normal cells. MSI-H results for either from deletion or insertion of repeating units attributed to defects in the DNA mismatch repair (MMR) system [8]. The MSI-H subgroup makes up approximately 15% of all CRCs and its prevalence is stage depeNDENT;15% of stage II–III CRC are MMR deficient (dMMR), it is less common in advanced stages and only 4–5% of stage IV CRC are dMMR [9,10]. The use of checkpoint blockade inhibitor therapy in this specific subset of CRC by now is the established treatment in the metastatic disease as first line and second line. In a phase II study by *Le et al.,* which evaluated the use of Pembrolizumab in patients with CRC who were both dMMR and pMMR. At 6 months follow up, the study reached its primary endpoint as the objective response rate was 40% dMMR patients with CRC. Additionally, the study demonstrated 90% disease control rate and 78% immune-related PFS in the dMMR CRC cohort as compared to the pMMR group in which no objective response rate was seen and the immune-related PFS was only 11%. Interestingly, only three out of 11 patients with LS associated CRC experienced an objective response compared to all six patients with sporadic dMMR had a response [11]. Patients with dMMR with Lynch syndrome are less responsive to immunotherapy than patients with sporadic dMMR patients and this is mostly due to the lower mutation burden in patients with Lynch syndrome [12]. There are more studies ongoing using checkpoint inhibitors in phase II and phase III evaluating the efficacy of these agents in patients with dMMR. In this study, we used checkpoint inhibitors in 3 patients, 2 colon and 1 rectal cancer, one of them with metastatic stage as palliative treatment, 1 as neo adjuvant before liver metastasis resection then as adjuvant and the 3rd one as neo adjuvant after chemo radiotherapy for rectal cancer; all of the 3patients showed dramatic response. The limitation of this study is the small number of patient (3 patients), it needs more studies with larger number of patients to confirm these finding.

9. Conclusion

Immunotherapy in dMMR in patients with CRC in different stages, metastatic disease, neo adjuvant and in postoperative setting with a very good outcome it is a small cohort of patient needs more larger study to confirm this finding. This finding needs larger study to confirm it.

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