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Case Report

Complete Response to Immunotherapy in a Patient with *MUTYH*-Associated Polyposis and Gastric Cancer: A Case Report

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Abstract
MUTYH-associated polyposis syndrome is an uncommon, autosomal recessive colorectal polyposis syndrome caused by biallelic inactivation of *MUTYH*. Most patients present with multiple colorectal polyps. However, other primary tumor sites have been described as less frequent. In this report, we describe the case of a young patient with a germline biallelic pathogenic MUTYH mutation with three different primary tumors. We focused on a metastatic gastric adenocarcinoma that presented with complete bowel obstruction secondary to extensive peritoneal carcinomatosis and achieved complete response upon treatment with immunotherapy. The patient's tumor presented with a high tumor mutational burden and a 100% combined positive score, which certainly contributed to the complete response to immunotherapy. To date, no studies have described the association of *MUTYH*-related tumors with high PD-L1 expression, but we hypothesized that it may be linked to the increased antigenicity of these cancers.

Introduction

MUTYH-associated polyposis (MAP) is an autosomal recessive colorectal polyposis syndrome caused by biallelic inactivation of *MUTYH.* The main clinical manifestations of affected patients are colorectal polyposis and colorectal cancer (CRC). In patients with

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multiple colorectal adenomas and no identifiable *APC* mutations, biallelic *MUTYH* inactivation can be found in 7–13% of those with >100 adenomas and 14–40% of those with 10–99 adenomas [1–4]. Usually, MAP patients develop 10–100 colorectal polyps by the fifth or sixth decade [5, 6] and have an increased lifetime risk for CRC (43%–63% at age 60 years, which may reach 80%–90% in the absence of proper surveillance) [7, 8]. Approximately 60% of MAP patients are diagnosed with CRC at presentation [7–13]. In a few MAP patients, CRC may develop in the absence of colorectal polyposis.

Germline monoallelic *MUTYH* alterations are common in the general population, reaching 1%–2% prevalence in northern European, Australian, and US populations. Biallelic alterations are much less common and account for <1% of individuals with the diagnosis of CRC [14, 15] but increases to 2% in young-onset CRC patients and to 10%–25% in CRC patients whose tumors harbor somatic KRAS c.34G>T (G12C) [13]. This association is linked to a distinct mutational signature in MUTYH-associated tumors, with prominent G:C>T:A transversions in NpCpA or NpCpT contexts [16].

Extracolonic manifestations of MAP are less frequently described. However, patients appear to have an increased risk of gastric and duodenal polyps [17, 18]. In one study that included 276 patients with MAP from 181 families, gastric and duodenal polyps were noted in 11 and 17 percent of patients, respectively. Higher risk for gastric cancer (GC) has been observed, although the trend was not significant [17]. In another cohort of 226 carriers of *MUTYH* germline alterations, increased risk for GC was identified only in monoallelic but not in biallelic mutation carriers [11]. Interestingly, patients with GC exhibiting low *MUTYH* expression seem to have a poor outcome when compared to those expressing high levels of *MUTYH* [19]. Furthermore, in a large European multicenter cohort of MAP patients, the incidence of extraintestinal malignancies was almost twice that observed in the general population (standardized incidence ratio 1.9; 95% CI: 1.4–2.5) with an overall lifetime risk of developing cancer of 38%. The estimated lifetime risk of cancers of the duodenum, ovaries, bladder, and skin was significantly higher as compared with the general population (4, 10, 6, and 17%, respectively) [17], and there is some evidence of an increased risk for breast and endometrial cancer. In addition, MAP patients may also present with thyroid nodules and benign adrenal lesions [20, 21], osteomas, congenital hypertrophy of the retinal pigment epithelium, dental cysts, desmoid tumors, sebaceous hyperplasia, and Muir-Torre phenotype with sebaceous gland tumors [22]. Here, we report a case (with the consent of the patient) of a young female patient with germline biallelic pathogenic *MUTYH* variants and diagnosis of advanced GC, who achieved complete clinical response to anti-PD1 therapy.

Case Report

Here, we report the case of a 21-year-old female patient with past medical history of depression and hypothyroidism with no family history of cancer. In July 2014, the patients were submitted to total colectomy due to a diagnosis of stage 3 CRC. During adjuvant oxaliplatin-based therapy for 6 months, the patient presented with a pulmonary nodule finding on routine thoracic imaging, which was biopsied, confirming an early-stage primary lung adenocarcinoma. The lung cancer was treated with surgical resection and adjuvant cisplatin and pemetrexed doublet. At that time, the patient declined genetic counseling and germline testing.

In October 2020, the patient presented with an intestinal sub-occlusion and was submitted to a segmental enterectomy due to an intestinal intussusception. The pathology report was consistent with an intramucosal adenocarcinoma of a hamartomatous dysplastic lesion. Two months later, the patient presented with yet another intestinal sub-occlusion. She underwent an upper endoscopy with a biopsy finding of a poorly cohesive gastric

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adenocarcinoma and strong immune infiltration, as shown in Figure 1. She was subsequently submitted to an exploratory laparoscopy with findings consistent with diffuse peritoneal involvement precluding surgical resection. Pathology reported a poorly cohesive, poorly differentiated carcinoma with a preserved expression of mismatch repair proteins on immunohistochemistry, as shown in Figure 2. Immunohistochemistry was performed on Autostainer Link 48 (Dako) using PT-Link Dako for antigenic retrieval and EnVision FLEX for visualization. Antibody (clones) included were MLH1 (ES05), PMS2 (EP51), MSH2 (FE11), MSH6 (EP49). Also, PD-L1 staining (DAKO 22C3 clone) showed combined positive score and tumor proportion score of 100% and 60%, respectively. Due to the intestinal sub-occlusion, the patient remained hospitalized with total parental nutrition due to incapacity of any oral ingestion.

Given the strong immune infiltration with high PD-L1 expression and considering patient's denial for any cytotoxic chemotherapy, the medical team decided to offer first-line therapy with pembrolizumab. A few weeks after initiating treatment in January 2021, the sub-occlusion was resolved, and parenteral nutrition was discontinued. The patient achieved complete clinical response in January 2023 and remains in complete remission until the present day (more than 1 year and 6 months), as shown in Figure 3.

To further characterize this spectacular response, the patient's gastric tumor samples were submitted to next-generation sequencing (NGS) with a broad panel of 180 genes (customized ArcherDX VariantPlex and FusionPlex, Oncoclínicas Precision Medicine) and revealed somatic mutations in *KRAS* (G12C), BRAF (G464V), PIK3CA (Q546K), SMAD4 (S474*), and MAP2K1 (K57 N). Based on NGS, tumor was classified as microsatellite stable (MSS) but had moderate to high mutational tumor burden (26.5 mutations per Mb). We also referred the patient to genetic counseling, and a germline NGS panel detected biallelic pathogenic *MUTYH* mutation (Y179C).

Discussion

The case reported here demonstrates for the first-time major response to immunotherapy in advanced GC of a patient harboring germline biallelic mutation in *MUTYH*. The *MUTYH* gene encodes for DNA glycosylase, a key enzyme in DNA base excision repair (BER) [23]. BER is responsible for correcting DNA alterations arising spontaneously from normal metabolic processes, lesions induced by chemical carcinogens, and abasic sites. *MUTYH* loss of function alterations leads to defective BER and an increased incidence of G:C to T:A transversions throughout the genome. The most commonly described germline loss of function *MUTYH* variants are Y179C (rs34612342) and G396D (rs36053993), which account for 75% of the reported mutations and are most prevalent in Caucasians [24–26].

MAP increases individual risks not only of CRC but also of extracolonic tumors such as ovarian, duodenal, and bladder cancers, which are usually diagnosed at younger ages as their sporadic counterparts [13]. The association of biallelic loss of function germline *MUTYH* alterations with GC remains still controversial. Although promising results of immunotherapy in MAP patients with CRC have been published, little is known about the response in those with non-CRC tumors.

MUTYH-associated tumors are characterized by a moderate mutator phenotype when compared to proficient mismatch repair CRC, with an average of 5.3 mutations per Mb. Despite being MSS, the higher mutation burden is associated with increased lymphocyte infiltration and frequent loss of HLA I class expression, suggestive of immune-driven selective pressure, resembling cancers with high-level microsatellite instability (MSI-H)

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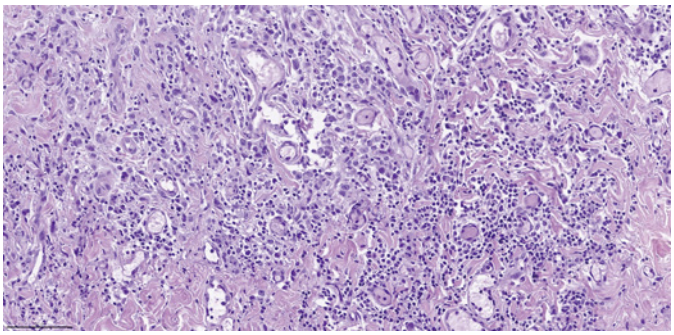

Fig. 1. Poorly cohesive adenocarcinoma (yellow arrows) admixed with abundant tumor-infiltrating lymphocytes (red arrows) in subperitoneal connective tissue (scale 50 μm).

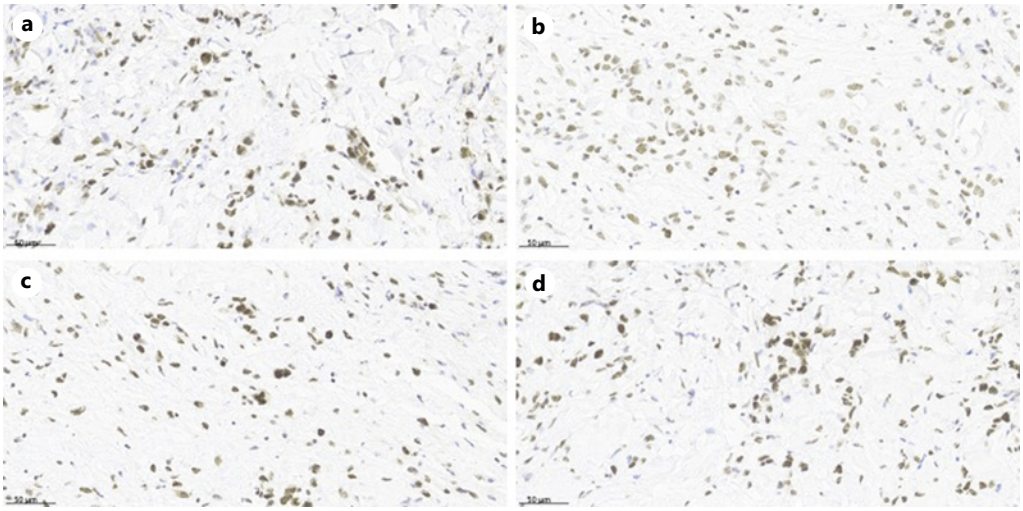

Fig. 2. Preserved expression of mismatch repair proteins (MLH1, PMS2, MSH2, MSH6) on immunohistochemistry. MHL1 (**a**); PMS2 (**b**); MSH2 (**c**), and MSH6 (**d**) (scale 50 μm).

[27–29]. High mutation burden and lymphocyte infiltration are known predictive markers for tumor response to immune checkpoint inhibitors, as seen in MSI-H CRC [30, 31]. Therefore, it has been hypothesized that tumors harboring *MUTYH* gene inactivation could be sensitive to immunotherapy, and 1 case report of patient with CRC harboring two mutations in *MUTYH* documented pronounced response to nivolumab therapy [29].

The mechanism to explain increased immunogenicity of high tumor mutational burden (TMB) cancers is believed to be related to the accumulation of so-called mutation-associated neoantigens, mutant proteins resulting from nonsynonymous mutations, which are strongly immunogenic. As previously stated, MUTYH-associated CRCs, although MSS, show a distinct mutational signature, with frequent G:C>T transversions and increased TMB combined with prominent lymphocyte infiltration [27, 32] which could render these tumors sensitive to therapy with immune checkpoint inhibitors [33, 34]. Indeed, our patient's poorly cohesive gastric tumor had moderate to high TMB and abundant lymphocyte infiltration. So far, no studies have described the association of *MUTYH*-related tumors with high PD-L1 expression, but we hypothesized that it may be linked to the increased antigenicity of these cancers, as in our case.

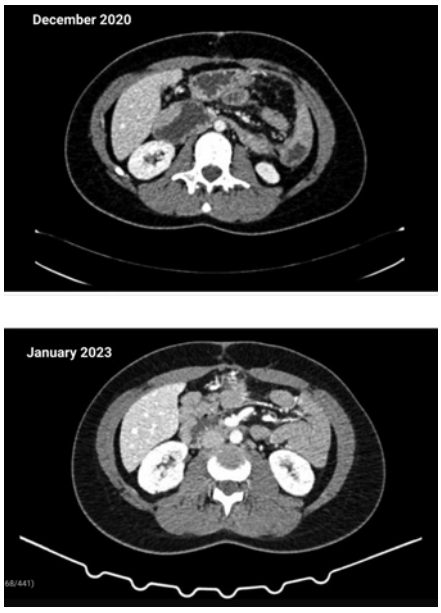

Fig. 3. Comparison of the patients' imaging studies (computerized topographies) from December 2020 prior to immunotherapy and January 2023 with immunotherapy (created with BioRender.com).

Interestingly, MAP patients with CRC may present a *KRAS* G12C transversion in up to 60% of the cases [27, 35, 36], which is most likely due to the intrinsic BER defect resulting in an accumulation of DNA transversions throughout the genome but especially in *APC* and *KRAS* [37]. Therefore, considering the low prevalence of *KRAS* G12C mutations in unselected CRC population (<4%) [38], it seems reasonable to consider screening these cases for germline *MUTYH* alterations. The same may be true for GC, as in our patient's case, given the extreme rarity of this genomic alteration in general (<1%) [39].

The present case contributes to the description of the MAP-associated phenotype with description of a very young patient diagnosed with three primary tumors. It contributes to the growing evidence for an association of MAP with GC and demonstrates that the impressive response to immunotherapy seen in patients with *MUTYH*-associated CRCs may also be achieved in other primaries, such as GCs. Due to the rarity of *MUTYH* cancers and the strong association with *KRAS* G12C somatic mutations, case reports like the one described here will increase awareness of the medical community on emerging genomic biomarkers of immunotherapy response beyond MSI and high TMB. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530965).

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. The patient described in the case report has given consent to publish this case, and written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

Maria Cecilia Mathias-Machado, Renata D. Peixoto, Patricia Ashton-Prolla, Leonard Medeiros Da Silva, and Rodrigo Dienstmann contributed to conception, research, and manuscript writing.

Data Availability Statement

The data that support the findings of this study are openly available in PubMed at https://pubmed.ncbi.nlm.nih.gov.

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