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Case Report

Fecal Microbiota Transplant for the Treatment of Metastatic Mesothelioma: A Case Report

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ABSTRACT

Malignant Pleural Mesothelioma (MPM) is a highly aggressive and almost universally fatal neoplasm with limited treatment options. The role of the programmed cell death protein 1 (PD-1) pathway has garnered attention due to its role in eliciting the immune checkpoint response of T cells, resulting in evasion of tumor cells from immune surveillance and chemotherapy resistance. Although, PD-1 checkpoint inhibitors have achieved success in various malignancies, resistance is common. Recently, the role of the gut microbiome in immunomodulation and response to cancer treatment has been recognized. We report a 70-year old female with stage 4 MPM who experienced restoration of therapeutic efficacy and prolonged survival with FMT and pembrolizumab despite prior antibiotic treatment, which is known to attenuate response.

Keywords: Malignant pleural mesothelioma; Trace elements; Safety; Pharmacoanalytics

INTRODUCTION

Malignant Pleural Mesothelioma (MPM) is an aggressive and fatal form of cancer associated with limited treatment options [1,2]. The median survival time post-diagnosis is 9 to 17 months with treatment [3], which is reduced to 6 to 9 months without treatment [4]. The sarcomatoid variant is the least common but most aggressive and treatment resistant of the three cell types, with a median survival time of ≤ 6 months despite therapy [5]. Standard treatment options for pleural mesothelioma include surgical resection, chemotherapy, radiation therapy, or a combination of these approaches [6]. In the past decade, programmed cell death protein-1 (PD-1) checkpoint inhibitors have emerged as a promising treatment option for various malignancies [7]. However, many fail to respond or develop acquired resistance to these therapies [8]. We report a case of a 70-year-old female with MPM who experienced tumor stability and prolonged survival following a combination of a PD-1 blockade inhibitor (pembrolizumab) and Fecal Microbiota Transplantation (FMT) to prevent acquired resistance.

CASE STUDY

A 70-year-old female presented with a 2-year history of metastatic mesothelioma of pleural origin, composed of 80% sarcomatoid and 20% epithelial subtypes. The patient complained of bloating, constipation, fatigue, flank pain, and significant weight loss (107 pounds). She had previously undergone right-side pleurectomy and decortication with adjunctive radiation as treatment for her mesothelioma. However, this had failed to halt disease spread and the patient subsequently developed bilateral renal masses, an intraabdominal node, and left lung metastasis. Biopsy of the renal masses confirmed metastatic mesothelioma. Due to the predominantly sarcomatoid cancer type, chemotherapy was not considered suitable due to the potential for adverse events and expected ~15% response rate [9]. Immunotherapy with pembrolizumab, a PD-1 blockade inhibitor was selected as first-line treatment on compassionate grounds given the disease stage and potential for enhanced response. However, the patient had received antibiotic treatment in the preceding months, which is known to attenuate anticancer activity and contribute to treatment resistance [8]. FMT was selected as adjunctive therapy due to concurrent gastrointestinal symptoms and potential modulation of response to immunotherapy [10].

An investigational new drug application was submitted to the Food and Drug Administration and the study was registered with ClinicalTrials.gov (NCT04056026). Prior to FMT, fecal and blood screening of the patient and donor (patient's 6-year old grandson) was performed, and a full medical history was collected.

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Screening of the donor stool included a gastrointestinal pathogen panel by PCR (Table 1) as well as carbapenem resistant Enterobacteriaceae, extended-spectrum beta-lactamase producing bacteria, *Helicobacter pylori* and vancomycin-resistant enterococci. Blood screening included a complete blood count with differential, presence of bacterial and viral pathogens (Table 2), lymphocyte subset panel (Table 3), and comprehensive metabolic panel.

Stool pathogen screening
Adenovirus F40/41
Astrovirus
Campylobacter
Clostridium difficile Toxin A and B
Cryptosporidium
Cyclospora cayetanesis
Escherichia coli 0157
Entamoeba histolytica
Enteroaggregative *E. coli*/EAEC
Enteropathogenic *E. coli*/EPEC
Enterotoxigenic *E. coli*/ETEC
Giardia lamblia
Norovirus GI/GII
Plesimonas shigelloides
Rotavirus A
Salmonella
Sapovirus
Shiga-like toxin *E. coli*
Shigella /Entero *E. coli*
Vibrio
Vibrio cholera
Yersinia enterocolitica

Table 1: Stool pathogen screening.

Blood panel screening
Complete blood count with differential
Comprehensive metabolic panel
Lymphocyte subset panel (Box 3)
Cytomegalovirus immunoglobulin G (IgG)
Epstein-Barr virus antibody panel
Entamoeba histolytica
Hepatitis A antibodies
Hepatitis B core antibodies
Hepatitis B surface antibodies
Hepatitis C antibodies
Human Herpesvirus-6 IgG
Human Immunodeficiency Virus antibody
Herpes Simplex Virus 1 and 2 IgG
Human T-Lymphotropic Virus Type I/II antibodies
IgE
Immunoglobulins Panel QT-IgG, IgM, IgA
John Cunningham virus antibodies
Strongyloides stercoralis antibodies
Syphilis serology

Table 2: Blood panel screening.

Blood panel screening
CD3 (absolute and percentage)
CD4 (absolute and percentage)
CD8 (absolute and percentage)
CD19 (absolute and percentage)
CD3-CD15+CD56 (absolute and percentage)
Lymphocytes (absolute)
CD4/CD8 ratio
CD, cluster of differentiation

Table 3: Blood panel screening.

The day prior to the procedure, the patient underwent bowel cleanse with sodium picosulfate/magnesium oxide/citric acid solution. On the day of the procedure, the patient was anesthetized and received 300 mLs of fresh stool slurry, prepared according to the Borody method [11], which was infused *via* the endoscopy channel.

The patient then received three cycles of pembrolizumab. For the following 8 weeks, the patient's tumours remained stable and the patient reported increased appetite and weight gain of one pound, in contrast with the previous trend of weight loss (Table 1). After 8 weeks, the patient developed a urinary tract infection, which required antibiotic treatment.

She subsequently developed concomitant infections that required further antibiotic treatment, but did not develop Clostridioides difficile infection. The patient developed chronic hematuria and anemia, and cystoscopy was performed.

The source was located to the left kidney, and left renal transarterial embolization was performed. Follow up PET/CT scan 7 months post-transplant revealed reduced standardized uptake value in the left lower lung lube, decreased to 4.2 from 5.3. Central portions of the left renal mass appeared necrotic; however, a peripheral portion remained viable. The right renal metastasis remained unchanged. The patient survived more than 29 months after her diagnosis, which is well outside the expected survival time of ≤ 6 months for the sarcomatoid variant [3] and thus is quite remarkable.

RESULTS AND DISCUSSION

Numerous drugs have been approved for the treatment of cancer that targets the PD-1 blockade, with many more in clinical trials [12]. Unfortunately, approximately 40%-45% of patients fail to respond to these therapies, and a further 30%-40% of initial responders go on to develop secondary resistance [13]. The gut microbiome has increasingly been implicated as one of the variables that may contribute to heterogeneity in response to cancer therapeutics, including PD-1 inhibitors. Sivan et al. demonstrated significant differences in melanoma growth rate and tumor-specific T cell responses between genetically similar mice harboring distinct commensal bacteria, which were ameliorated following cohousing or fecal transfer [14]. Interestingly, oral administration of *Bifidobacterium* significantly slowed tumor growth and increased tumor-specific T cell responses and infiltration of antigen-specific T cells into the tumor to the same degree as PD-L1 blockade. However, combination treatment using both fecal transfers from mice with the less aggressive melanoma phenotype and anti-PD-L1 antibodies further improved tumor control and circulating tumor antigen–specific T cell responses. In a separate study, the same authors evaluated stool samples collected from 42 patients with metastatic melanoma prior to immunotherapy, including PD-L1 treatment, to determine biomarkers of response [15]. A significant association was observed between commensal microbial composition and clinical response, with *Bifidobacterium longum, Collinsella aerofaciens and Enterococcus faecium* bacterial species more abundant in responders. Reconstitution of germ free mice with fecal material from responders was associated with improved tumor control, augmented T cell responses, and superior efficacy of anti-PD-L1 therapy. In a study evaluating the oral and gut microbiome in 112 patients with melanoma undergoing anti-PD-1 immunotherapy, significant differences in the diversity and composition of the gut microbiome was observed in patients with improved response to anti-PD-1 immunotherapy and prolonged progression-free survival versus nonresponders [16]. In particular, responders demonstrated significantly higher alpha diversity ($P<0.01$) and relative abundance of bacteria of the Ruminococcaceae family ($P<0.01$), including Clostridiales/Ruminococcaceae/Faecalibacterium, which were positively correlated with CD8+ T cell infiltrate in the tumor and higher levels of effector CD4+ and CD8+ T cells in the systemic circulation. In contrast, non-responders had a higher abundance of Bacteroidales, shortened PFS, and a higher level of Tregs with a blunted cytokine response. Recently, a phase 1 clinical trial was conducted to assess the safety, feasibility, and immune cell impact of FMT and reinduction of anti-PD-1 immunotherapy in patients with refractory metastatic melanoma [17]. The two FMT donors selected had previously been treated with anti-PD-1 monotherapy for metastatic melanoma and had achieved a complete response for at least 1 year. A total of 10 patients with metastatic melanoma had confirmed progression on at least one line of anti-PD-1 therapy and were considered eligible for transplant. In terms of safety, the only observed FMT-related Adverse Event (AE) was mild bloating between days 3 and 15 in one recipient. Several mild (grade 1) immune-related adverse events were observed, mainly arthralgia. No moderate-to-severe immune-related adverse events (grades 2 to 4) were observed, although five recipients had developed such immune-related adverse events during their previous anti–PD-1 treatment lines. FMT is now a widely accepted treatment for recurrent Clostridioides difficile colitis [18], with a well-established safety profile [19,20] and its safety has consistently been demonstrated even in immunocompromised patients [21] Nevertheless, the lack of FMT-related complications in this study and others among immunocompromised metastatic patients treated with repeated FMTs is reassuring.

CONCLUSION

In our case, manipulation of the gut microbiome *via* FMT facilitated successful treatment with pembrolizumab and was associated with prolonged survival. These findings support a direct link between the gut microbiome and the efficacy of immunotherapy to treat metastatic mesothelioma. Given the lack of treatment options and poor prognosis for MPM, FMT may have potential as an adjunct to immunotherapy, to restore bacterial diversity within the gut and stimulate an immune response from within the patient. However, additional, larger-scale studies are warranted to further investigate these remarkable, albeit preliminary, observations.

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