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Fecal transplantation in patient with metastatic melanoma refractory to immunotherapy: A case report

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Abstract

BACKGROUND

Immunotherapy has revolutionized the treatment of metastatic melanoma, but a significant proportion of patients still experience treatment resistance. Fecal microbiota transplantation (FMT) has emerged as a potential strategy to overcome immunotherapy resistance by modulating the gut microbiome.

CASE SUMMARY

We present a case report of a 57-year-old male with metastatic melanoma refractory to immunotherapy who received FMT in combination with anti-PD-L1 immunotherapy (pembrolizumab). After failing multiple lines of treatment, the patient underwent a single FMT procedure by colonoscopy using fecal material from a female metastatic melanoma donor who successfully responded to immunotherapy. Following FMT, the patient demonstrated a response with decreased subcutaneous disease and subsequently underwent surgery to remove the residual disease. Despite a subsequent recurrence in the small bowel that was resected, the patient remained on pembrolizumab without evidence of melanoma recurrence at the time of writing.

CONCLUSION

The favorable clinical and long-lasting effect we saw in our patient without significant toxicity suggests that this procedure should be considered in similar patients with immunotherapy refractory melanomas.

INTRODUCTION

Melanoma accounted for 325 000 new cases worldwide, causing about 57 000 deaths in 2020 (1), affecting males more frequently than females. It is estimated that Melanoma cases should increase by 50% in 2040, reaching 510 000 new cases and 96 000 deaths (1). Despite the recent remarkable advances in the treatment of metastatic melanoma with immunotherapy and anti-Braf targeted therapies, about 40% of the patients will still die of their disease (2,3).

One possibility treating immune-refractory patients with metastatic melanoma is the manipulation of the gut microbiome through Fecal Microbiota Transplantation (FMT) (4–6). FMT can restore sensitivity to anti-PDL1 immunotherapy in about 40% of patients previously refractory to this medication (5,6). **Based on these encouraging preliminary data (5,6), we report here a case of a 57-year-old patient refractory to immunotherapy who benefited from FMT added to Anti-PD1 immunotherapy with Pembrolizumab, to which he was previously refractory.**

CASE PRESENTATION

Chief complaints

We report the case of a 57-year-old man without any significant previous medical history with metastatic BRAF V-600E mutated melanoma diagnosed in October 2019 and started on Nivolumab with a partial response. In October 2020, we noted **disease progression** in the subcutaneous tissue of the right thoracic region, and we started Cobimetinib and Vemurafenib without a response. In December 2020, we **started** Ipilimumab plus Pembrolizumab with a new progression. The Pembrolizumab was maintained, and in April 2021, he received only FMT by colonoscopy without prior antibiotic therapy. **Fecal material was obtained from a female metastatic melanoma**

patient donor who achieved a longstanding complete response to Ipilimumab and Nivolumab and was off therapy in remission for more than 2 years. The donor had an entirely negative pre-donation screen for multiple infectious agents. The patient and donor formally consented to the FMT procedure.

After FMT, as seen in Figure 1, the right lateral thoracic subcutaneous disease decreased in size while we maintained Pembrolizumab. In September 2021, the patient underwent surgery to remove the residual disease. In July 2022, he had a PET scan that showed a small intestinal loop with increased FDG uptake, and we also noted a decrease in the ferritin level. A small intestinal survey with an endoscopic capsule revealed an abnormality in the small intestine judged as a melanoma recurrence which was resected and confirmed by the pathological report. As there were no other foci of disease, we maintained Pembrolizumab **until this writing (06/23/2023) and the patient is presently in remission without evidence of melanoma recurrence.**

2

History of present illness

See Above

History of past illness

See above

Personal and family history

N/A

Physical examination

N/A

Laboratory examinations

See above

Imaging examinations

See above

FINAL DIAGNOSIS

See above

TREATMENT

See above

OUTCOME AND FOLLOW-UP

See above

DISCUSSION

+ADw-html+AD4APA-p+AD4-The gut microbiome represents a highly dynamic environment where diet, medication intake, or emotional stress can induce significant changes (7). There are strong correlations between the gut microbiome and the nervous and immune systems (7). Intestinal dysbiosis occurs when there is a disturbance in the complex commensal microbial communities in the digestive tract, including the overgrowth of certain microorganisms (e.g., bacteria or fungi). Existing evidence has shown that gut dysbiosis may contribute to the etiology of numerous human diseases (7,8), including diabetes, atherosclerosis, inflammatory bowel disease, atopic dermatitis, autism, or even cancer development. Furthermore, mice with tumors but no gut microbiome showed different responses when treated with cancer immunotherapy (7,8).+ACY-nbsp+ADsAPA-/p+AD4-

+ADw-p+AD4-Several authors showed that FMT could circumvent immunotherapy resistance in metastatic melanoma patients rendering about 30+ACU- to 40+ACU- of them susceptible again to anti-PD1 agents to which they were resistant (4,5). The mechanism whereby FMT can restore sensitivity to anti-PD1 monoclonal antibodies is not completely understood. Davar +ADw-i+AD4-et al+ADw-/i+AD4- demonstrated

that FMT induced rapid and durable changes in the gut microbiota. The responders showed increased abundance of certain taxa associated with response to anti-PD-1, increased activation of CD8⁺ T cells with higher cytolytic functions, and decreased frequency of interleukin-8-expressing myeloid cells which may have immunosuppressive activity (5). Proteomic and metabolomic analyses revealed distinct signatures in the responders, and network analyses confirmed that the gut microbiome regulated these changes (5). In addition, Baruch +ADw-i+AD4-et al+ADw-/i+AD4- (4) reported that gut sample analysis demonstrated post-treatment up-regulation of gene sets related to APCs +ADw-i+AD4-via+ADw-/i+AD4- MHC class 1 and IL-1 mediated signaling. Furthermore, tumor sample analysis showed post-treatment up-regulation of multiple immune-related gene sets (Interferon- γ ADs-, T cell activation, MHC Class II protein complex, dendritic cell differentiation, and T helper 1 type immune response)(4).+ACY-nbsp+ADsAPA-/p+AD4-

+ADw-p+AD4-Our patient had disease resistant to Nivolumab, Pembrolizumab (anti-PD1 monoclonal antibodies), and Ipilimumab (an anti-CTLA4 monoclonal antibody). After FMT, Pembrolizumab, to which its disease was resistant, regained its effectivity, as seen by the decrease of his right lateral thoracic subcutaneous disease. We did only one FMT by colonoscopy without prior antibiotic treatment, as did Davar +ADw-i+AD4-et al+ADw-/i+AD4- (5). Baruch +ADw-i+AD4-et al+ADw-/i+AD4- (4), however, did serial FMTs in the patients they treated by capsules or colonoscopy and used antibiotics pre-FMT. If more than one procedure is needed, whether colonoscopy or capsules may be the best way of doing the FMT, and if antibiotic pretreatment is needed, all require further research. +ACY-nbsp+ADs-In addition, both Davar +ADw-i+AD4-et al+ADw-/i+AD4- (5) and Baruch +ADw-i+AD4-et al+ADw-/i+AD4- (4) reported changes in the microbiome of patients who underwent FMT and did not show any significant toxicity due to this procedure. +ACY-nbsp+ADsAPA-/p+AD4-

+ADw-p+AD4-This report has limitations. Besides the fact that we reported here one only case of restoring sensitivity to anti-PD1 treatment through FMT, we also did not

pursue immunological studies or fecal microbiome analysis.

CONCLUSION

Despite these limitations, the favorable clinical and long-lasting effect we saw in our patient without significant toxicity suggests that this procedure should be considered in similar patients with immunotherapy refractory melanomas.

ORIGINALITY REPORT

9%

SIMILARITY INDEX

PRIMARY SOURCES

- 1 www.ncbi.nlm.nih.gov 63 words — 5%
Internet
- 2 Xiao-han Wang, Jia-qian Zhang, Qi Kong, Wen-zhen Tu, Li-ming Chen, Yin-huan Zhao. "Application of Integrated Traditional Chinese and Western Medicine in Treatment of Systemic Sclerosis: A Case Report", EXPLORE, 2022 26 words — 2%
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