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Letter to the Editor

Diet-dependent toxicity of ipilimumab in metastatic melanoma

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Dear Editor,

The anti–cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody ipilimumab is approved by the Food and Drug Administration (FDA) as one of the main therapeutic agents for treatment of melanoma [1,2]. Its use can lead to long-term remission but also risks inducing immune-related side effects [3]. Although most adverse events are mild, the most common severe and potentially life-threatening adverse event is the development of gastrointestinal toxicity. Common terminology criteria for adverse events (CTCAE) ≥ grade 2 diarrhoea occurs in 35% of patients treated with ipilimumab, including cases of severe colitis and bowel perforation requiring colectomy [1,4]. Median onset of gastrointestinal symptoms is eight weeks after initiation of immune checkpoint inhibitor therapy [5]. Patients who progress after initially benefitting from ipilimumab treatment can be re-treated with the anti–CTLA-4 antibody, because data show that re-treatment can provide lasting disease control for a second time. The frequency of immune-related adverse events observed during re-treatment has been found to be similar to that observed during the first treatment, and adverse events in re-treatment usually occur without the incidence of new types of toxicities [6]. Factors predicting the risk of toxicity in patients have been less thoroughly investigated, and research focuses primarily on biomarkers predicting clinical response. Various baseline factors associated with treatment-related toxicity have been proposed. Patients with an already-elevated calprotectin level in stool before treatment had a higher risk of colitis. Moreover, high serum interleukin-17 (IL-17) levels have been shown to be significantly associated with the risk of severe immune-mediated diarrhoea. However, further research in this field is required [7–9]. We report the case of a patient who tolerated the first treatment with ipilimumab (four cycles) well but developed severe gastrointestinal toxicity leading to hospitalisation during re-treatment with ipilimumab. Ipilimumab was administered at the same dosage, and we could not find any differences between the circumstances of the initial ipilimumab and re-treatment cycles, except that the patient entirely changed his day-to-day dietary habits between the two cycles. This is, to our knowledge, the

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first report on severe gastrointestinal toxicity in ipilimumab re-treatment after previously well-tolerated same-dose therapy.

1. Case report

A 51-year-old male patient presented at our outpatient clinic at the Section of Dermato-Oncology of the National Center for Tumor Diseases, Heidelberg, in 2014 after local excision of a gluteal melanoma and subsequent left inguinal lymph node dissection. In 2015, advanced stage IV disease (with left inguinal tumor mass and new lung metastases) was diagnosed. A biopsy of inguinal lymph nodes confirmed the relapse, and molecular analysis revealed no mutation in the BRAF and NRAS genes. The patient was treated with four cycles of ipilimumab, at a dose of 3 mg/kg body weight every three weeks. After the first two cycles of ipilimumab, our patient developed dysphagia caused by a growing retropharyngeal metastasis, and local radiation (50 Gy) was therefore also applied. After completion of four ipilimumab cycles, the patient's metastases significantly decreased in size, leading to partial remission which lasted for more than two years (Fig. 1). During and after this first treatment phase, no signs of immune-related adverse events were recorded. In 2017, he developed a single progressive metastasis in the vastus lateralis muscle, which was again treated by radiotherapy because an excision was not easily possible. All other lesions including those of the lung and pharynx were stable. After radiation, we decided on re-treatment with ipilimumab because this had previously controlled the disease for two years and had been very well tolerated. This time, after two cycles of ipilimumab the patient developed severe diarrhoea (CTCAE grade III), which required discontinuation of therapy and patient hospitalisation. Laboratory analysis showed an increase in C-reactive protein (CRP) from a normal range to 98.6 mg/l. Stool samples revealed no evidence of pathogens but did show an increase of calprotectin up to 1800 µg/g. Proctosigmoidoscopy was performed and showed inflammation of the bowel in terms of a moderate proctosigmoiditis (Fig. 2). Human cytomegalovirus (CMV)-induced colitis was discounted twice. A FDG-PET scan highlighted a significant tracer uptake in the rectosigmoid (Fig. 1), in agreement with the radiological

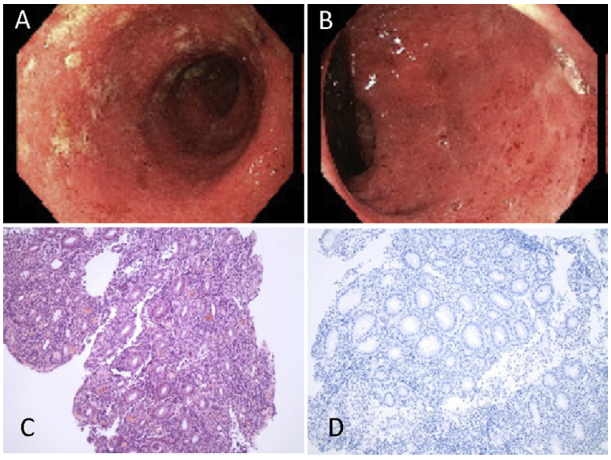

Fig. 2. Endoscopic appearance of colitis with submucosal bleeding and small ulcerations (A, B). Histologic examination confirmed a lymphocytic infiltration compatible with autoimmune colitis (C) and no proof of CMV (D).

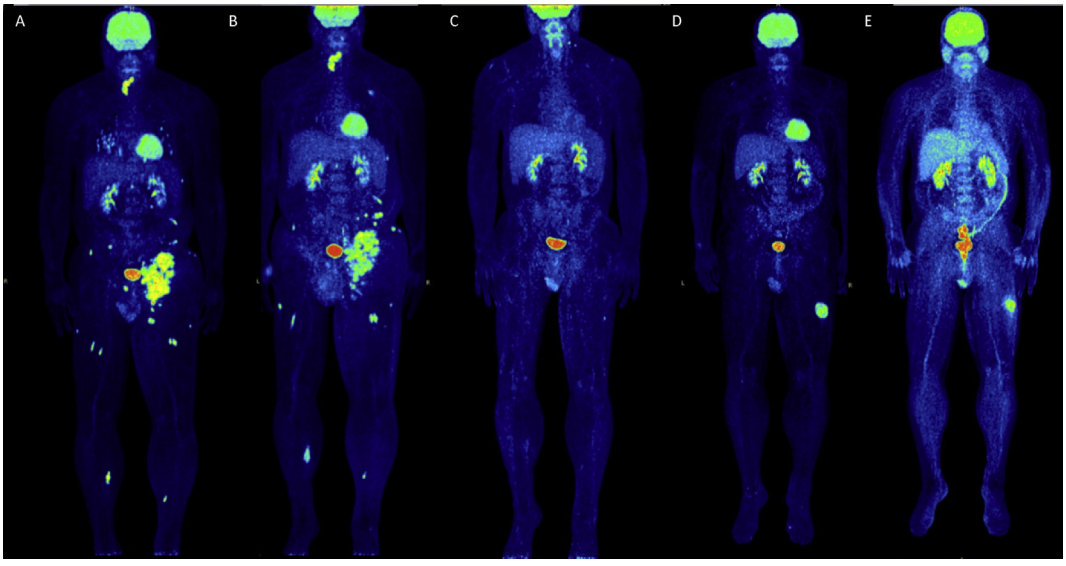

Fig. 1. PET/CT scans before (A), after two cycles (B) and after four cycles (C) of initial ipilimumab treatment; the patient achieved a complete remission by ipilimumab, of note no signs of colitis. (D) PET/CT before retreatment with ipilimumab showing one progressing metastasis at the left vastus lateralis muscle which was radiated. (E) PET/CT after 12 weeks of ipilimumab reinitiation shows a stable disease and signs of colitis. PET, positron-emission tomography; CT, computed tomography.

image of colitis. In conclusion, therapy-induced immune-related colitis was diagnosed. We treated the patient with systemic steroids, initially by means of oral application of prednisolone 1 mg/kg body weight because the patient refused hospitalisation. In the absence of improvement after eight days, we admitted the patient to our inpatient clinic, applied methylprednisolone 2 mg/kg body weight IV, and after three days without improvement, added mycophenolate mofetil (MFM) 3 g per day because the patient was concerned about infliximab treatment. The patient received total parenteral nutrition and fluids. This combination treatment had no clinical effect and resulted in a further increase in stool frequency and bloody stool after 12 days; because of this, we then applied a one-time infusion with infliximab 5 mg/kg body weight. This finally led to an improvement in symptoms and we could slowly and gradually reduce the immunosuppressive medication. Eleven months after the second ipilimumab treatment, the patient's disease is now stable, and complete resolution of his colitis has been achieved.

The only noteworthy difference found between the patient's condition before initial ipilimumab treatment and before re-treatment was with respect to the patient's diet. During the initial ipilimumab treatment course, our patient claimed to follow a strict self-proclaimed alkaline diet [10], which consisted of preferably natural unprocessed food and was high in fruit, vegetables and fish and low in meat. In addition, the consumption of sugar, alcohol, coffee, dairy and white flour products was avoided entirely. Nutrition was supplemented with barley grass and unpeeled millet. No probiotics or antibiotics were used. After achieving a remarkable clinical benefit from the initial ipilimumab treatment, our patient discontinued the 'alkaline diet' and went back to 'normal eating habits'. Hence, his diet during re-treatment with ipilimumab did not follow any specific rules or food restrictions and thus allowed daily consumption of alcohol (mainly beer), meat, white flour products, dairy, sugar and processed food. No antibiotic treatment was taken before ipilimumab treatment and re-treatment. Our patient could not recall any other changes in behaviour or lifestyle when comparing the initial and re-treatment phases. Stool frequency and consistency were also normal during initial treatment and before re-treatment. Our patient had no relevant pre-existing conditions except for bronchial asthma and did not take any oral medication except for occasional use of analgesics. Medical imaging after ipilimumab re-treatment with two additional cycles again showed that his disease was stable.

2. Discussion

The CTLA-4 inhibitor ipilimumab can cause mild-to-severe toxicities [3]. The most common severe and sometimes life-threatening immunotherapy-related toxicities are of gastrointestinal origin [1,4]. If patients are re-treated with ipilimumab, studies have shown that tolerability is similar compared with initial treatment. No new toxicities occurred with re-treatment, and toxicities observed during initial treatment did not predispose patients to re-treatment toxicity in a clinical phase III trial [6]. Our case report demonstrates an example of high toxicity during re-treatment after a previously well-tolerated treatment with ipilimumab. Recently, a similar patient case has been reported in which a patient developed life-threatening colitis during ipilimumab re-treatment despite good tolerance of the initial treatment. The authors concluded that this probably resulted from the higher dosage of ipilimumab at re-treatment. The patient had initially received ipilimumab at a dose of 3 mg/kg (four doses in combination with nivolumab followed by two doses continued treatment with nivolumab) and two months later at a dose of 10 mg/kg as monotherapy [11]. Remarkably, in our patient we observed similarly severe colitis with ipilimumab re-treatment, although ipilimumab was given at the same dose. Because colitis typically develops early on during ipilimumab treatment, it seems unlikely that it was caused simply by a possible cumulative effect of additional ipilimumab doses. In addition, although our patient had received radiotherapy to the thigh before ipilimumab re-treatment, it is unlikely that this induced the colitis, because the bowel was not in the radiation field and he had also received radiation during the first ipilimumab treatment. In addition, previous studies could find no association between increased ipilimumab toxicity and radiation therapy [12,13]. At re-treatment, our patient received ipilimumab in an adjuvant setting because the only detectable metastases had been radiated previously. Because a high dose of ipilimumab was given in the adjuvant trial [14], however, it cannot be judged if adjuvant therapy itself leads to increased toxicity. Instead, tolerability in our patient changed with a different diet, suggesting that various factors affect tolerability of immunotherapy.

Ipilimumab-related colitis often clinically and histologically resembles other inflammatory bowel diseases such as ulcerative colitis [15]. It is known that nutrition and diet can affect prevention of symptoms and treatment of inflammatory bowel diseases [16–19]. Recent data have shown a connection between checkpoint inhibitor–associated colitis in particular and the composition and dynamics of the intestinal microbiome [20]. Increased representation of bacteria belonging to the Bacteroidetes phylum have been correlated with resistance to the development of checkpoint blockade–induced colitis. In contrast, Firmicutes species have been associated with the development of colitis [21]. The microbiome of the intestine can in turn be modified by substantially changing nutritional habits. Fibre and distinct phytochemicals in particular have been shown

to affect the gut microbiome and to have anti-inflammatory effects. In addition, strong immunomodulatory effects have been found for quantitative variations in nutrition uptake, particularly overeating and fasting. The composition of the diet can also have anti-inflammatory effects, e.g., a high amount of omega-3 fatty acids contained in nuts and fish. It has been suggested that other substances, such as N-glycolylneuraminic acid, which is particularly abundant in beef, have proinflammatory effects [22]. When our patient tolerated ipilimumab well, his diet was rich in fish and low in meat; this aspect of his diet at least would agree with these to-date unproven theories. Thus, the high toxicity in the presented case is most likely related to changes in our patient's diet which might have affected bowel integrity and the intestinal microbiome. Unfortunately, stool samples were not collected before treatment to prove this.

In conclusion, our patient case demonstrates that even if treated with the same dose, tolerability of immunotherapy can differ substantially in re-treatment. The development of adverse events, therefore, seems to depend on various factors, including the significant effect of diet. Further research is needed to explore the effect of different diets on immunotherapy. Interestingly, the composition of the intestinal microbiome not only affects adverse events but has also been shown to relate to treatment response [21–26]. It has not yet been thoroughly investigated whether diet significantly affects treatment efficacy of immunotherapy.

Conflict of interest statement

Jessica C Hassel has had a paid consulting role with Merck and Amgen and has received honoraria from Bristol-Myers Squibb, Merck, Novartis, Roche and Pfizer. Alexander Enk has had a paid consulting role with MSD and Lilly and has received honoraria from Bristol-Myers Squibb, Biotest and Novartis. All other authors declare no conflict of interest.

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