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Original Research

Cytomegalovirus reactivation in patients with refractory checkpoint inhibitor-induced colitis☆

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Abstract ***Objectives:*** Immune checkpoint inhibitors can cause severe immune-related adverse events, with immune-related diarrhea and colitis (irColitis) being among the most frequent ones. While the majority of patients with irColitis respond well to corticosteroid treatment ± other immunomodulatory drugs such as infliximab, some patients do not show resolution of their symptoms. In the present study, we analysed the frequency of therapy-refractory irColitis, the underlying cause, and useful diagnostic approaches.
Methods: Between 2006 and 2016, 370 patients with metastatic malignant melanoma were treated with checkpoint inhibitors at the Department of Dermatology at the University Hospital Essen. All patients were identified for whom diarrhea and/or colitis was documented in the digital patient records. Patients who did not respond to standard immunosuppressive therapy within 2 weeks were classified as refractory. Demographic and clinical data of all patients were collected.
Results: We identified 41 patients with irColitis, the majority occurring during treatment with ipilimumab. Amongst these, 5 (12.2%) were refractory to standard immunomodulatory

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treatment with corticosteroids and infliximab. Therapy-refractory cases tended to show more severe inflammation in colonic biopsies ($p = 0.04$). In all therapy-refractory cases cytomegalovirus (CMV) was detectable. CMV-DNA in colonic biopsies and in plasma was significantly more often detectable in therapy-refractory cases (in colonic biopsies $p = 0.005$, in plasma: $p = 0.002$). Presence of serum CMV IgM and positive immunohistochemical stainings of colon biopsies for CMV were also associated with refractory colitis ($p=0.021$; $p = 0.053$).
Conclusions: This report on CMV reactivation during management of checkpoint inhibitor-induced colitis emphasises the need for repetitive diagnostic measures in treatment-refractory irColitis.

1. Background

Recently, monoclonal antibodies directed against different immune checkpoints have revolutionised the therapy of locally advanced and metastatic malignant melanoma and other human malignancies. The anti-CTLA-4 antibody ipilimumab, the anti-PD-1 antibodies nivolumab and pembrolizumab as well as the combination of ipilimumab and nivolumab have shown increased progression-free and overall survival in several clinical studies in patients with advanced melanoma [1–6]. While unleashing the immune system is the desired anti-tumour effect that helps the patient's own immune system to fight the tumour cells, checkpoint inhibitors can also cause severe immune-related adverse events (irAEs) such as immune-related diarrhea and colitis (irColitis) [6] by directing the immune system against own 'healthy' tissue. Causing up to 9.3% of all grade 3/4 (according to CTCAE version 4.03) irAE, diarrhea is one of the most frequent high-grade irAE of checkpoint inhibitor therapy [6].

Immunosuppressive drugs are used to manage irAE according to common treatment algorithms. High doses of steroids are considered standard treatment for severe irColitis [7]. In irColitis refractory to corticosteroids after 5–7 days, other immunosuppressive drugs such as infliximab are used [8]. Nevertheless, in some patients diarrhea and colitis do not improve while on immunosuppressive treatment. However, the frequency and pathogenesis of refractory irColitis (i.e. refractory to corticosteroids and infliximab) remain elusive. To this end, we retrospectively reviewed data of 370 patients treated with checkpoint inhibitors at the Department of Dermatology at the University Hospital in Essen between 2006 and 2016, identified all patients who experienced irColitis and analysed if they responded to standard immunosuppressive therapy.

2. Methods

2.1. Patient cohort

The skin cancer database of the Department of Dermatology of the University Hospital Essen was searched for melanoma patients treated with either ipilimumab, nivolumab, pembrolizumab or the combination of ipilimumab plus nivolumab between 2006 and 2016. Demographic as well as clinical data were collected for all identified patients. Digital patient records were then searched for the terms 'diarrhea' and 'colitis'. Severity of irColitis was graded according to CTCAE version 4.03 criteria and clinical parameters were analysed (clinical symptoms, duration of colitis and stool frequency). End of irColitis was defined as stool frequency returning to baseline. Data on treatment of irColitis was collected. Patients not returning to baseline stool frequency within 2 weeks while on immunosuppressive therapy were considered as refractory to standard immunosuppressive therapy. Diagnostic procedures to assess irColitis were documented. Collection of patient samples was performed after informed consent and approval by the local ethics committee.

2.2. Histopathology and immunohistochemistry

Colonic biopsies were taken during colonoscopies before and during treatment of diarrhea and colitis. From all biopsies, haematoxylin and eosin (H&E) stains were evaluated. Tissue samples were tested by PCR and immunohistochemistry (IHC) for cytomegalovirus (CMV) according to institutional standards to rule out CMV infection (for further information see supplementary file).

2.3. Detection of CMV-DNA and CMV-specific antibodies

Blood samples were taken before and during treatment of diarrhea and colitis to rule out a CMV infection. CMV-DNA and CMV-specific antibodies were quantified in these samples according to institutional standards (see supplementary file).

2.4. Statistical analysis

Statistical analysis was performed by applying the Chi-square test, fisher's exact test or Mann–Whitney test as