Case Reports in Gastroenterology

Case Rep Gastroenterol 2021;15:97–99

DOI: 10.1159/000511750
Published online: January 26, 2021

Letter to the Editor

Response to "Cytomegalovirus Enterocolitis in a Patient with Refractory Immune-Related Colitis"

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Dear editor,

With great interest we read the case report by Furuta et al. [1] concerning cytomegalovirus (CMV) as cause of continuing enterocolitis in a patient with immune checkpoint inhibition-related colitis (ICIRC). The authors describe a patient with steroid-refractory ulcerative colitis after treatment with nivolumab and ipilimumab. After finding positive immunohistochemistry for CMV in colonic biopsies but no antigenemia, the patient was treated with ganciclovir while methylprednisolone was tapered. A protracted clinical recovery followed, with hematochezia caused by bleeding ileal ulcers persisting for a few weeks.

By presenting this case the authors address an important potential side effect of immune checkpoint inhibitors: colitis by reactivation of CMV. One should keep in mind that the diagnosis of CMV colitis is not straightforward, as is how to determine the clinical relevance. In the majority of patients with ulcerative colitis, CMV is considered an innocent bystander [2, 3]. On the other hand, CMV may be harmful mainly in steroid-refractory colitis, as CMV may result in more frequent relapse and higher colectomy rates [4]. We previously described two cases of steroid-refractory ICIRC with signs of CMV infection [5]. In one of the cases histology showed many CMV-positive cells on immunohistochemistry, fecal CMV DNA was positive, and the viral load was high (42,000 copies/mL). Due to a prolonged course of colitis even with ganciclovir, diagnostics were repeated and showed decreased levels of CMV in serum as well as in biopsies. The patient recovered after increasing the dose of prednisolone to 2 mg/kg (she had been treated with infliximab earlier during the admission). The second case of steroid- and infliximab-refractory ICIRC also showed signs of CMV, but this concerned only a few CMV-positive cells on histology and a viral load of 356 copies/mL. In this case CMV was not considered relevant and antivirals were therefore not administered. Remission was obtained after starting tacrolimus. The first case and the one presented by Furuta et al. support that CMV can be an important factor in refractory ICIRC. However, our second case supports previous literature

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that the CMV load needs to be high in order to be considered clinically relevant. In our opinion, it is important to determine and report the CMV load in biopsies and serum. CMV infections where both histology and serum viral load only show low levels of CMV appear not to be relevant, and one can refrain from antivirals but increase or alter immunosuppressants in refractory cases instead. However, cases with many CMV-positive cells on histology and/or cases with high serum viral load suggest clinically relevant CMV infection, and we prefer treatment with ganciclovir in these cases. In our experience, probably >50 CMV-positive cells in a single biopsy sample are needed in order to consider the CMV infection relevant. This threshold is not evidence-based though and requires further research. Wethkamp et al. [6] previously suggested that IBD patients with >600 CMV copies/10^5 cells (obtained from biopsy samples) were likely to respond to antiviral therapy and lower numbers suggested latent infection. Furuta et al. do not report information on the load of CMV-positive cells. Improvement may have occurred because of ganciclovir if high levels of CMV were present. On the other hand, as hematochezia persisted 14 days after starting ganciclovir, the enterocolitis might as well have been the result of steroid-refractory ICIRC, and increasing the dose of methylprednisolone or starting infliximab might have resulted in (earlier) improvement. The improvement of the described patient after starting ganciclovir and without increasing methylprednisolone could also have occurred due to the prolonged effect of methylprednisolone. In that situation CMV would be associated with ICIRC without causality. Still, the relevance of CMV remains difficult to determine, and clinicians prescribing immune checkpoint inhibitors and treating ICIRC should be aware of the possibility of CMV infection, especially in steroid-refractory cases.

Conflict of Interest Statement

None of the authors have any conflict of interest by publishing this paper.

Funding Sources

Not applicable.

Author Contributions

S. van Turenhout drafted the manuscript and developed the concept of this letter to the editor. P. Snaebjornsson and J. van Dieren performed critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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