Reviewer's report

Title: Chronic Diarrhea associated with Persistent Norovirus Excretion in Patients with Chronic Lymphocytic Leukemia: Report of Two Cases

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Reviewer: Timm H. Westhoff

Reviewer's report:

The authors describe two cases of chronic symptomatic norovirus infection in patients suffering from chronic lymphocytic leukemia and hypogammaglobulinemia. The authors speculate that one patient died as “a direct cause of chronic diarrhea” (Abstract). The paper is well written.

The case report may be of interest for the readers of BMC Infectious Diseases since it gains further insight in the problem of norovirus infection in immunocompromised subjects. Whereas norovirus infection in immunocompetent individuals is an unpleasant but usually harmless self-limiting disease of short duration, norovirus infection can cause severe chronic diarrhea with signs of malnutrition in immunocompromised subjects. To date, norovirus-induced chronic diarrhea has been described in solid-organ recipients (heart transplant recipient, pediatric intestinal transplant recipients, renal transplant recipients, lung transplant recipients), hematopoietic stem cell recipients/bone marrow transplantation, and HIV patients. Furthermore, there is case series on pediatric patients with hematological and oncological disorders including AML, ALL, rhabdomyosarcoma and neuroblastoma (Ludwig et al, J Med Virol. 2008). The present report on chronic norovirus infection in CLL adds another piece of the puzzle.

Major revisions:

The authors should present an overview on the conditions in which chronic norovirus infection has been described so far (either in Introduction or in Discussion).

The authors report on ongoing diarrhea as a symptom of norovirus infection. Did the patients present the classical symptoms of nausea and vomiting as well? Did these symptoms persist or did they occur only at the beginning? What about fever?

Due to the chronic shedding of the virus the patients have to be regarded as infectious. Were there any cases of acute gastroenteritis in the patients’ environment? There is an ongoing debate on how to manage hygienic requirements in chronic norovirus shedding. What did the authors do? “Chronic isolation”?

Both patients underwent endoscopic examinations. Did the authors gain deep
duodenal biopsies for exclusion of celiac disease and M. Whipple? If so, they should provide a description/images of the corresponding histology. Can they provide data on intraepithelial lymphocytes? In immunocompetent subjects, norovirus infection induces a rapid increase in intraepithelial lymphocytes (Troeger et al., Gut 2009). In transplant recipients with chronic symptomatic norovirus infection, however, CD8+ intraepithelial T cells have been shown to be only in (high) normal range (Westhoff et al., NDT 2009) as a potential cause of the reduced ability to clear the virus. The authors should discuss the immunological reasons for the lack of viral clearance in their cases of CLL. Is it due to the CLL itself or due to immunosuppressive treatment? Are there any therapeutical consequences?

In the abstract the authors state that both patients died, one of them due to chronic diarrhea. In the text, however, one patient died from pneumonia and septic shock. The other patient “has continuous symptoms at the time of writing” and therefore fortunately appears to be alive. Please clarify.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No conflict of interest