Sodium Polystyrene Sulfonate and Cytomegalovirus-Associated Hemorrhagic Duodenitis: More than Meets the Eye

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient:	**Male, 56**
Final Diagnosis:	**Hemorrhagic duodenitis**
Symptoms:	**Abdominal pain • melena**
Medication:	**—**
Clinical Procedure:	**CT scan • gastroscopy • colonoscopy • blood transfusion**
Specialty:	**General and Internal Medicine**

Objective: Challenging differential diagnosis

Background: Hemorrhagic duodenitis is an exceptionally rare adverse event of sodium polystyrene sulfonate (SPS) treatment and is a common manifestation of cytomegalovirus (CMV) reactivation. SPS is known to cause marked inflammation in the lower gastrointestinal tract, including colonic necrosis, whereas involvement of the small bowel is uncommon. Although its effectiveness and safety has been disputed since its introduction, SPS remains widely used due to lack of alternatives. CMV infection and reactivation are well-known complications after solid-organ transplantation, particularly in seronegative recipients receiving organs from seropositive donors, and is associated with significant morbidity and mortality. The lower gastrointestinal tract is more commonly involved, but infections of all parts of the intestine are observed.

Case Report: Here, we report the case of a 56-year-old man who presented with severe upper-gastrointestinal bleeding. Hemorrhagic duodenitis was initially attributed to the use of SPS, as abundant SPS crystals were detected in the duodenal mucosa but we found only 2 CMV-infected endothelial cells. Two weeks later, gastrointestinal bleeding recurred. However, this time, abundant CMV-infected cells were demonstrated in the duodenal biopsies.

Conclusions: Our case report highlights an uncommon adverse event after SPS use with a simultaneous CMV reactivation. The main difficulty was to differentiate between CMV reactivation and CMV as an "innocent bystander". This demonstrates the challenge of decision-making in patients with complex underlying diseases.

MeSH Keywords: Cytomegalovirus Infections • Duodenitis • Hyperkalemia • Kidney Transplantation
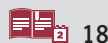
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Background

Hyperkalemia is commonly observed in renal transplant recipients with several contributing factors, such as treatment with calcineurin inhibitors, trimethoprim, or angiotensin-converting enzyme inhibitors, but treatment options are limited [1,2]. Since 1958, sodium polystyrene sulfonate (SPS) has been widely used for management of acute and chronic hyperkalemia. Initially, it was combined with sorbitol to prevent constipation and fecal impaction. However, an increasing number of case reports showing severe adverse events, such as colonic necrosis, led to the use of SPS without or with only a small amount of sorbitol [3]. Despite (or because of) its long track record for the treatment of hyperkalemia, the pharmacological safety and effectiveness of SPS in reducing serum potassium levels have never been accurately defined. Interestingly, the controversy over the effectiveness of SPS in the management of hyperkalemia is still ongoing, particularly as there are promising new therapies on the horizon, such as patiromer and sodium zirconium sulfonate [4–6].

In contrast to the abundant case reports documenting severe adverse events in the lower gastrointestinal tract, SPS-related toxicities in the upper-gastrointestinal tract have been rarely described in the literature [7–9].

After renal transplantation, reactivation and infection with various pathogens are a major concern of treating physicians. CMV infection/reactivation is associated with significant morbidity and mortality in renal transplant patients [10]; therefore, guidelines recommend CMV serological screening for all organ donors and recipients. If donor and recipient are seronegative, no prophylaxis is required. In case of a seronegative recipient receiving organs from a seropositive donor and in seropositive recipients, international guidelines recommend antiviral prophylaxis or preemptive therapy [11]. Antiviral prophylaxis is associated with lower all-cause mortality, particularly in high-risk patients [12].

CMV infection/reactivation often presents with non-specific symptoms, such as fever, night sweats, and fatigue, before symptoms of organ involvement predominate. Apart from antiviral prophylaxis, regular monitoring of the CMV viral load in plasma or whole blood and pre-emptive treatment have become an accepted strategy after solid-organ transplantation in order to avoid a tissue-invasive disease and its consequences. Infection of the gastrointestinal tract is the most common manifestation of CMV disease after kidney transplantation, with the lower gastrointestinal tract affected in the majority of cases [13,14]. A diagnosis of CMV enteritis/colitis may be confirmed with CMV nucleic acid testing of the blood in a patient with signs and symptoms compatible with gastrointestinal CMV disease. Occasionally, histopathological examination

of tissue specimens may be required, in particular in patients with unusual signs or a negative CMV nucleic acid test. The presence of cytoplasmic inclusions and nuclear enlargement with eosinophilic nuclear inclusions are classic indicators of tissue-invasive disease. Immunohistochemical tests targeting CMV antigens are applied to increase sensitivity and specificity. Management includes antiviral treatment with ganciclovir or valganciclovir, and reduction of immunosuppressive treatment, if possible.

Case Report

A 56-year-old male patient presented to the Emergency Department with a 1-day history of sharp lower-abdominal pain and melena. His past medical history included chronic renal failure requiring hemodialysis secondary to type 2 diabetes mellitus and severe arterial hypertension, and dyslipidemia. Three weeks before, he had received a kidney transplant from a deceased child donor and was treated according to our standard immunosuppressive regimen including basiliximab on day 1 and 4, mycophenolate, tacrolimus, and prednisolone. The initial post-transplant course was complicated by a local hematoma that was evacuated, delayed graft function secondary to tubular necrosis, and metabolic acidosis with hyperkalemia that required ongoing treatment with sodium bicarbonate and SPS. Besides immunosuppressive, hypertensive, and diabetic therapy, his discharge medications included acetylsalicylic acid and pantoprazole. As the patient was seropositive and the donor was seronegative for CMV, a strategy of regular monitoring of CMV viral load and preemptive therapy was employed in accordance with national and international guidelines.

On presentation, the patient was afebrile and blood pressure and heart rate were 107/44 mmHg and 58 bpm, respectively. Physical examination was significant for right lower-quadrant abdominal tenderness. Routine blood tests demonstrated profound anemia (hemoglobin 57 g/l; norm: 140-180), lymphocytopenia (0.22×10^9/l; norm: 0.9–3.3), hyperglycemia (20.8 mmol/l; norm: 3.8–6.1), hyperkalemia (7.0 mmol/l; norm: 3.6–4.8), and an elevated serum creatinine (249 µmol/l; norm: 49–97). Venous blood gas analysis was significant for metabolic acidosis (pH 7.30; norm: 7.38–7.42, bicarbonate 14.7 mmol/l; norm 21–26). In a non-contrast abdominal CT scan, the distal part of the small bowel and the colon were filled with hyperintense fluid, consistent with gastrointestinal bleeding (Figure 1). The patient immediately received 2 packed red blood cell (PRBC) transfusions (and 4 additional PRBC during the first week of admission) and was transferred to the Intensive Care Unit for monitoring and further treatment. Insulin with glucose was administered and SPS was continued. On the following day, gastroscopy demonstrated severe ulcerative duodenitis with no
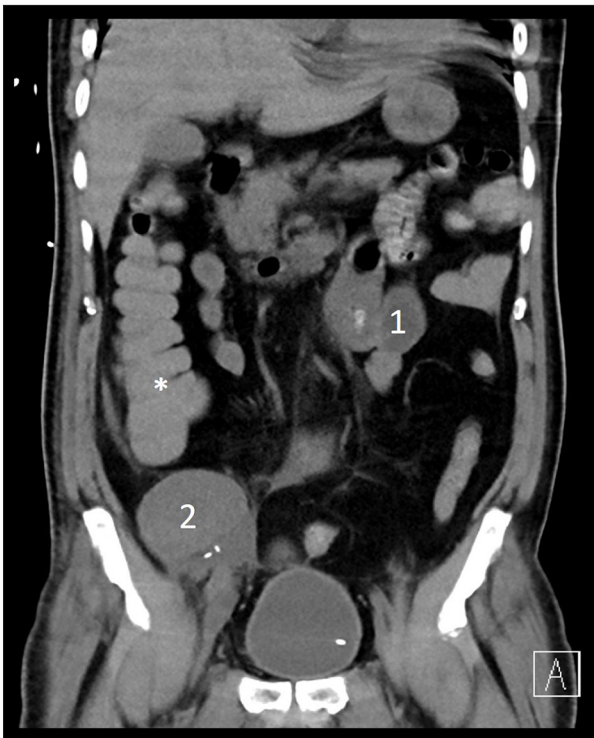
Figure 1. Non-contrast abdominal CT scan demonstrating hyperintense fluid in the ascending colon (asterisk), consistent with gastrointestinal hemorrhage. The small bowel (1) and cecum (2) are also depicted.

Figure 2. Gastroscopy image of the duodenum on the second day of admission, showing severe ulcerative duodenitis without active bleeding.

Figure 3. Biopsy taken from a duodenal ulcer on the occasion of the first gastroscopy, showing polygonal purple SPS crystals (asterisks) embedded within the fibrinoleukocytic exudate. (HE; 100×).

evidence of active bleeding (Figure 2). Colonoscopy was normal. Histological work-up of gastric and duodenal biopsies revealed a severe erosive duodenitis. Abundant SPS crystals were detectable within the fibrinoleukocytic exudates of the duodenal ulcers and on the surface of the inconspicuous gastric mucosa (Figure 3). In addition, 2 CMV-infected endothelial cells were detected by CMV-immunohistochemistry in the same duodenal biopsies. Given the presence of abundant SPS crystals, the rather small number of detectable CMV-infected cells in the biopsy and the presence of a stable low-level viremia (Figure 4) led to the decision to withhold antiviral treatment. SPS treatment was ceased immediately after the first gastroscopy, and treatment for hyperkalemia was continued with insulin/glucose infusions and inhaled beta-2 agonists [15]. Additionally, treatment with fludrocortisone was initiated due to suspected hyporeninemic hypoaldosteronism [16,17]. Despite immediate cessation of SPS and lack of ongoing melena, the patient's hemoglobin slowly decreased during the next 2 weeks, at which point he again developed profound melena (Figure 4). Repeat gastroscopy confirmed extensive ulcerative duodenitis as the most likely source of gastrointestinal bleeding, with continuous involvement of the jejunum suspected. In contrast to the first episode, histopathology of duodenal biopsies revealed abundant enlarged endothelial and stromal cells with characteristic intranuclear and cytoplasmic inclusions corresponding
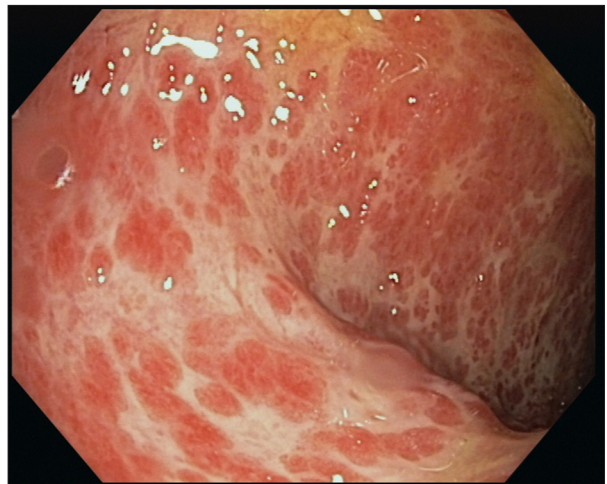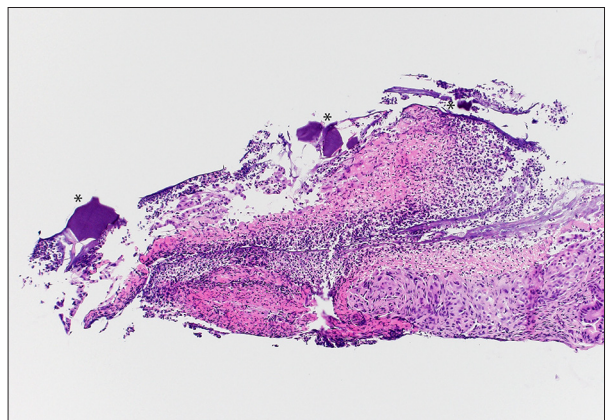
to CMV-infected cells. Immunohistochemistry allowed the detection of even more cells, including epithelial cells, containing CMV antigens (Figure 5). At this point, CMV PCR in the peripheral blood was positive with 1585 IU/ml (norm: <137) and peaked in the following days at 14491 IU/ml. After diagnosis of CMV duodenitis, antiviral treatment was initiated with ganciclovir for 5 days and continued with valganciclovir [12]. The CMV viral load became undetectable 22 days after initiating antiviral treatment, and gastrointestinal bleeding ceased. Valganciclovir was continued as secondary prophylaxis. Three months later, renal function had stabilized with creatinine levels of approximately 130 μmol/l (estimated glomerular filtration rate 50 ml/min/1.73 m^2), and, importantly, no further complications have occurred.
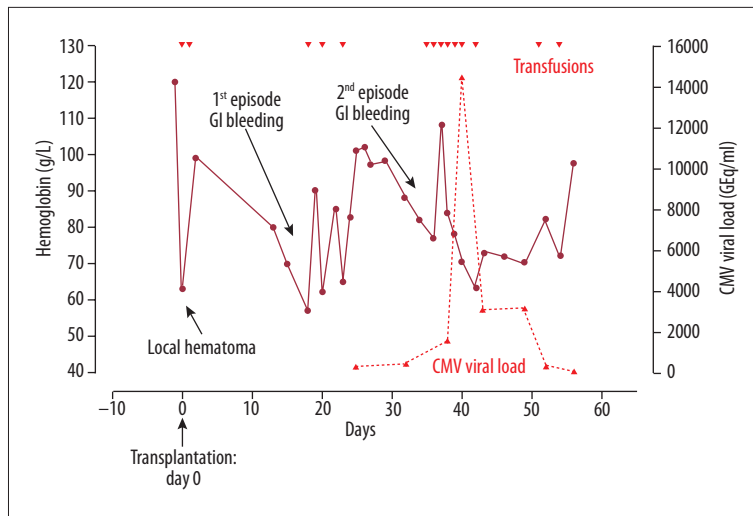
Figure 4. Course of hemoglobin and CMV viral load in the present patient.
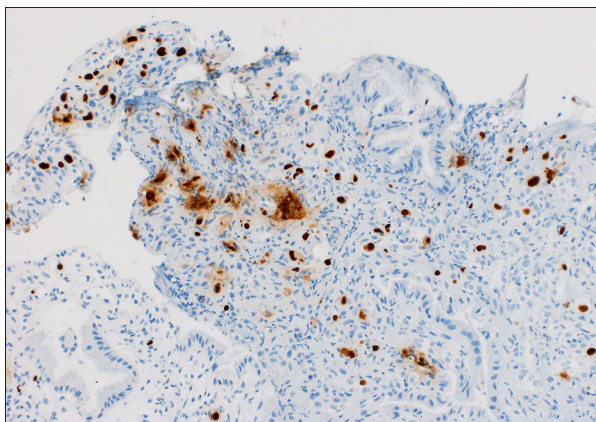

Figure 5. Detection of CMV intranuclear inclusions by immunohistochemistry in numerous mesenchymal and epithelial cells in a biopsy taken from a duodenal ulcer on the occasion of the second gastroduodenoscopy. (FLEX Monoclonal Mouse Anti-Cytomegalovirus, Clone CCH2 + DDG9, Dako, Denmark; 200×).

Discussion

In the present case, detection of SPS crystals in the duodenal mucosa with concomitant inflammation in the setting of severe ulcerative duodenitis was suggestive of SPS-induced gastrointestinal toxicity leading to severe blood loss. The patient received a total of 17 PRBCs over the course of 5 weeks, which underscores the severity of gastrointestinal bleeding in this patient. However, despite absence of overt bleeding, the subsequent clinical course with a slowly decreasing hemoglobin and a second severe bleeding episode 2 weeks later was indicative of an additional pathology, and severe CMV upper-gastrointestinal disease was confirmed on repeat gastroscopy. As there was already weak evidence of CMV infection in the first biopsy, one might argue that SPS was only an "innocent bystander" and disguised the real cause of mucosal inflammation. However, initial biopsies were consistent with SPS-induced inflammation of the duodenum rather than CMV organ disease given the profound ulcerations and profound gastrointestinal bleeding, although we cannot exclude a sampling error. Additionally, major bleeding stopped almost immediately after cessation of SPS, whereas it most likely would have continued if CMV disease was the real culprit causing initial upper-gastrointestinal bleeding. In our opinion, the CMV reactivation was most likely a secondary event in the setting of a severe illness (similar to the observed disease in critically ill patients [18]) and ongoing immunosuppression. Retrospectively, however, immediate initiation of antiviral treatment at the first evidence of CMV-infected cells in the duodenal biopsy in a patient with gastrointestinal bleeding and profound inflammation would have been advisable.

Conclusions

Renal transplant recipients are at increased risk for adverse events in the early post-transplant period, including infections, graft rejection, and medication adverse effects. Adverse events associated with the use of SPS and in the setting of CMV reactivation are well known but may appear in uncommon locations. CMV infection/reactivation should always be considered early as a differential diagnosis among renal transplant recipients presenting with non-specific symptoms. Due to the potential adverse events of SPS, particularly during long-term therapy, alternative treatment options may be considered.

Conflict of Interest

None.

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