Transpl Int (1998) 11 [Suppl 1]: S242–S244

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CMV infection detected in the upper gastrointestinal tract after liver transplantation

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Abstract As a pilot series on the frequency of gastroduodenal cytomegalovirus (CMV) involvement after liver transplantation, we examined forceps biopsies of 13 consecutive patients who underwent esophagogastroduodenoscopy during the first 3 months after transplantation. CMV was demonstrated in frozen sections by monoclonal antibody and immunoperoxidase staining. In parallel, peripheral blood was examined for CMV pp65 antigenemia. CMV antigens were detected in biopsies of ten patients, in ten cases in the duodenum and in four in the stomach. At the time of endoscopy, sic patients had CMV antigenemia, five of them had a simultaneous positive finding in the duodenum. Although all ten patients with the positive biopsy finding had some gastrointestinal symptoms, only one had severe enteritis. In liver transplant patients, CMV was commonly detected in leukocytes located in the mucosa of the upper gastrointestinal tract, especially in the duodenum. Further investigation is needed to determine the significance of positive CMV findings in the biopsies and their association with the development of severe gastrointestinal symptoms.

Key words CMV · Upper gastrointestinal tract · Liver transplantation

Introduction

Cytomegalovirus (CMV) is considered to be the single most important pathogen in patients after organ transplantation. After liver transplantation, CMV infection involving the allograft, lungs, and other organs is a substantial cause of morbidity and mortality. In the gastrointestinal tract, CMV causes ulcerations, erosions, and mucosal hemorrhage [1]. Nausea, abdominal pain, and diarrhea are common clinical symptoms of gastrointestinal CMV infection. Only scarce information is available on CMV infection of the gastrointestinal mucosa. The objective of this study was to screen how often CMV is found in gastroduodenal biopsies and what are the special features of CMV infection in the mucosa.

Patients and methods

CMV was examined in forceps biopsies of 13 consecutive adult patients (8 women, 5 men) who underwent esophagogastroduodenoscopy during the first 3 months after liver transplantation. Etiology of the liver disease was acute fulminant hepatitis in four, chronic liver disease in seven, and malignancy in two patients. Esophagogastroduodenoscopy was performed within 3 months after the transplantation. All patients received azathioprine, cyclosporine, and methylprednisolone as immunosuppressive treatment and all were preoperatively CMV seropositive. Indications for the endoscopy were gastrointestinal symptoms in seven patients, CMV antigenemia with minor gastroduodenal symptoms in three patients, and control endoscopy of preoperatively found lesions in three patients.

The biopsies were snap-frozen and 3-μm-thick sections were cut. CMV was demonstrated in the frozen sections of two parallel samples taken from the duodenum and stomach. A monoclonal antibody against CMV-specific antigens (pp65; Biotest Pharma, Frankfurt, Germany) and immunoperoxidase staining were used. In parallel, peripheral blood was examined for CMV pp65 antigenemia [5].

Table 1 Cytomegalovirus *(CMV)* findings in 13 patients after liver transplantation

Patient number	CMV in the duodenum	CMV in the stomach	CMV antigenemia
1	+	+	+
2	+	–	–
3	+	+	+
4	+	–	–
5	–	–	–
6	+	–	+
7	–	–	+
8	+	–	–
9	+	–	–
10	+	+	+
11	–	–	–
12	+	+	–
13	+	–	+

Results

CMV was detected in the biopsies of ten patients. All of them had a positive finding in the duodenum, and four also had a positive finding in the stomach. CMV findings of all patients are demonstrated in Table 1. At the time of endoscopy six patients had CMV antigenemia, five of them also had positive findings in the biopsies. On the other hand, in five patients CMV was found only in the gastrointestinal tract.

One of the patients (number 3) had severe gastrointestinal symptoms with diarrhea, nausea, and abdominal pain associated with CMV infection and six patients had gastroduodenal symptoms, i.e., nausea, postprandial pain, heartburn. Patients with positive finding in the stomach were included in this group. All patients with positive CMV findings in the gastroduodenal mucosa complained of some upper gastrointestinal symptoms, part of which were unspecific.

Macroscopical and microscopical findings in the endoscopy were minor. None of the patients had *Helicobacter pylori* or NSAID-associated gastroduodenitis. In patients with positive CMV findings in the stomach, mucosa in the antrum was edematous, but no ulcerations or erosions were found, only minor inflammatory infiltration was seen. In the gastroduodenal mucosa, CMV was found in mononuclear and polymorphonuclear leukocytes, but not in mucosal cells. Positive leukocytes were found both in the superficial and deep layers (Fig. 1).

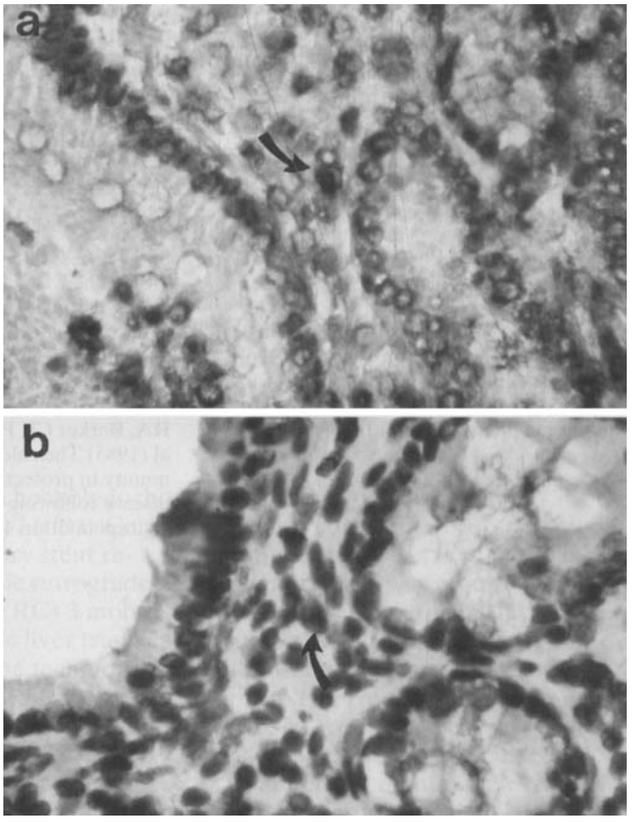

Fig. 1 Cytomegalovirus was detected in leukocytes both in the deep (**a**) and in the superficial (**b**) layers of the duodenum

Discussion

In liver transplant patients, CMV was commonly detected in the gastrointestinal mucosa, especially in biopsies from the duodenum. Characteristically, in the present patients, of whom only one had significant gastrointestinal symptoms, CMV was found in leukocytes in all layers of the gut, but not in tissue cells. In severe gastrointestinal CMV disease the major infected cell types were found to be epithelial cells, endothelial cells, and smooth muscle cells [3]. Thus, infected leukocytes might represent a preliminary stage which can lead to outbreak of gastrointestinal CMV disease.

Currently, when screening for CMV, antigenemia is feasible and immediate antiviral treatment is available; severe gastrointestinal CMV disease is uncommon in liver transplant patients. Before specific antiviral drugs were available, CMV caused gastrointestinal ulcerations with massive bleeding and perforations with a high mortality rate [4]. Nowadays, nausea and impaired gastric emptying due to edema in the pylorus are found to be the most common, characteristic symptoms of upper gastrointestinal CMV infection [6]. Half of our patients had these kind of symptoms, which can also be side effects of immunosuppressive drugs or antibiotics. Furthermore, CMV infection is found to change intestinal permeability, which can lead to impaired absorption of immunosuppressive drugs and, consequently, to a higher risk of acute rejection [2].

In conclusion, in liver transplant patients, CMV was commonly detected in leukocytes located in the mucosa of the upper gastrointestinal tract, especially in the duodenum. These patients were asymptomatic or had only mild upper gastrointestinal symptoms. Further investigation is needed to determine the significance of a positive finding in the gastroduodenal biopsies in association with duodenal manifestations and the development of severe gastrointestinal symptoms.

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