EXPERIENCES OBTAINED WITH UPPER PANENDOSCOPY IN ORGAN TRANSPLANT RECIPIENTS WITH SPECIAL REGARD TO CYTOMEGALOVIRAL INFECTIONS OF THE UPPER GASTROINTESTINAL TRACT

Doctoral theses

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Introduction

Mild or more severe gastrointestinal signs and symptoms occur in 80 to 90% of post-transplant patients for more or less time, and 30 to 80% of them require invasive diagnostics and therapy. 10% of the complications are very serious and may even lead to loss of the graft or death of the recipient. Gastrointestinal haemorrhages of post-transplant patients belong to this group.

Patients who underwent organ transplantation may develop several gastrointestinal conditions which can hardly be observed in patients receiving no immunosuppression, and a significant part of these are of infectious origin. Cytomegalovirus (CMV) is one of the most frequent and most dangerous infections of immunosuppressed post-transplant patients affecting 44 to 85% of recipients of kidney and liver transplantation. Symptomatic CMV disease develops in a considerable part of infected patients.

The gastrointestinal tract is one of the main target organs of tissue-invasive CMV infections. According to data of the literature, gastrointestinal CMV disease develops in 5 to 15% of organ transplant recipients, but the number of asymptomatic infections is certainly substantially higher, it may even reach 30 to 40%.

CMV may cause ulceration, erosions and mucosal haemorrhage in the mucosa of the gastrointestinal tract. These phenomena alone are not specific, but the infection can be confirmed if an appropriate method for detecting the virus is found. The key for the diagnosis of CMV infection includes detection of the virus, a specific constituent particula of it, or the consequences of the viral infection. There are considerable differences in the specificity and sensitivity of the individual methods. Gastrointestinal CMV infection can be confirmed when the identification of the virus is done from the area of the GI tract.

An outstanding field in professional literature on gastroenterology and endoscopy deals with the endoscopic diagnosis of upper gastrointestinal haemorrhage and analysis of the possibilities for endoscopic haemostasis. We can find very few data, however, on

experiences with emergent upper endoscopic examination and haemostasis in a special patient population, namely recipients of organ transplantation.

Objectives

1. Establishing a protocol for upper panendoscopic examinations performed at the Endoscopic Laboratory of the Department of Transplantation and Surgery in patients who underwent organ transplantation; analysis of the data from the endoscopies, and comparison between findings of kidney or liver recipients.

2. Diagnostics of cytomegalovirus infection in the upper part of the gastrointestinal tract, evaluation of CMV infections demonstrated by endoscopic examination; determination of the clinical importance of demonstrated infections.

3. Evaluation of urgent upper panendoscopic examinations performed because of a haemorrhage; comparison of data with non-transplant patients; comparison of findings in kidney and liver recipients who were examined because of a haemorrhage.

Methods

1. Patients and Methods of Upper Panendoscopies Performed in Organ Transplant Recipients

Between the 1st of January 1998 and the 31st of December 2007 we performed a total of **656 upper panendoscopies in 431 patients** that is a significant number considering the great number of patients receiving care at the outpatient clinics of our department (as on the 31st of December 2007 a total of 1673 patients including 1417

kidney, 241 liver and 11 pancreas + kidney recipients as well as 1 heart and 3 lung recipients) examined in the frame of consultations.

The endoscopic examinations were performed by two very experienced members of our department with qualifications in surgery and gastroenterology. Endoscopic morphological alterations were evaluated on the base of the same principles.

According to our protocol, endoscopies were always associated with sample taking by biopsies from the following areas:

(1) at least 3 samples from a circumscribed lesion of the oesophagus-stomach (if it was present);
(2) at least 3 samples from the gastric antrum, 2 samples from the area in front of the pylorus by 2 to 3 cm, (1 sample each from the greater and lesser curvatures), and 1 sample from the angle of the stomach;
(3) at least 2 samples from the gastric body, from the areas of the greater and lesser curvatures; and
(4) at least 2 samples from the first part of the duodenum.

No tissue sample was taken in the following cases:

(1) during examinations performed because of an existing or suspected haemorrhage;
(2) in patients receiving anticoagulation therapy;
(3) in patients with a disorder of coagulation;
(4) and when the patient gave no consent to the biopsy.

Histological examinations of biopsy samples were performed at the 1st Institute of Pathology and Experimental Cancer Research of the Semmelweis University. General light microscopic examination of the samples was performed with haematoxylin-eosin staining. Samples of gastric tissue underwent modified Giemsa staining for detection of Helicobacter pylori. Qualitative PCR examinations were also performed from each sample in order to detect CMV-DNA.

The average age of the examined patients was 49.8 (16 to 76) years. 54.1% of them were male. 84.9% and 13.9% of patients undergoing endoscopy were kidney and liver recipients respectively (in addition

we also examined 3 pancreas + kidney, 3 lung and 1 heart recipients).

The patients received 41 different maintenance immunosuppressive regimes; the most frequently used combinations were: cyclosporine + mycophenolate + prednisolone (151 patients) and tacrolimus + mycophenolate + prednisolone (79 patients).

A third of the endoscopies were performed within the first year after transplantation, another third between 1 and 5 years, and the further third beyond 5 years.

In the second part of our general analysis we compared the data of upper panendoscopies performed in 483 kidney and 79 liver recipients. No significant differences were found between the demographic data of the two groups of patients.

2. Patients and Methods in the Diagnostics of Cytomegalovirus Infections of the Upper Gastrointestinal Tract

Detection of signs of CMV infection from biopsy specimens was performed at the 1st Institute of Pathology and Experimental Cancer Research of the Semmelweis University. "Conventional" histological examination was based on a search for cells showing cytomegaly during light microscopic examination of biopsy specimens stained with haematoxylin-eosin. Three diagnostic criteria had to be fulfilled concomitantly:

1. Cells with diameters at least threefold larger than normal;
2. Homogeneous eosinophilic intracellular ("owl's eye") inclusion bodies;
3. Granular intracytoplasmic inclusions.

From the same samples, qualitative PCR examinations were performed in order to detect CMV-DNA. Details of the methodology used:

Tissue samples from endoscopy were fixed by formalin and then embedded into paraffin. Paraffin was removed with xylol and ethanol, and the samples underwent digestion by 100 µg/ml proteinase K at 50°C for 12 hours. For terminating digestion, samples were heated to 90°C for 10 minutes. Undiluted samples were diluted to tenfold, and then 1 µl of them was amplified in Red Taq mix (Sigma) with end volume of 25 µl, according to the prescriptions of the manufacturer.

The PCR product of 179 base pairs was detected on 2% agarose gel. Cloned CMV sequences were used as positive controls.
The GB 1 and GB 2 primers recognise the glycoprotein B gene of CMV.
The sequences were:
GB 1 50-GAG GAC AAC GAA ATC CTG TTG GGC A-30
Sense
GB 2 50-GTC GAC GGT GGA GAT ACT GGT GAG G-30
Antisense
As for the studied case, patients were considered to have CMV infection if CMV DNA could be identified in any of their samples examined.

3. Patients and Methods in the Analysis of Data from Urgent Upper Panendoscopies Performed in Organ Transplant Recipients

Between the 1st of January 1994 and the 31st of December 2007 a total of 3362 panendoscopies were performed at the Endoscopic Laboratory of the Department of Transplantation and Surgery; in 796 (23.7%) and 2566 (76.3%) patients with and without organ transplantation respectively.

Within the processed 14 years a total of 393 urgent upper panendoscopies were performed, adding up to 11.7% of all examinations. We performed a total of 133 urgent upper endoscopic examinations in 101 organ transplant recipients. With the exception of one examination due to acute oesophageal obstruction, indication

of urgent endoscopy was present or suspected upper gastrointestinal haemorrhage. Further on we deal only with analysis of cases examined due to a haemorrhage.

In patients with localised active haemorrhages and in case of sources of bleeding with a high risk of rebleeding (e.g. Forest II/a, II/b stage bleeding ulcers, "cherry red spot" on the surface of an oesophageal varix) we attempted endoscopic haemostasis in all patients. Of the possibilities of endoscopic haemostasis the following were feasible for us:

1. Sclerotisation

Oesophageal varices were sclerotised with 1 to 2% polidocanole (Aethoxysklerol®) with perivasal technique, using 1.5 to 2 ml per injecting points. The total volume of medicine used in one session did not exceed 20 ml. In a part of cases, particularly when we observed significant oozing haemorrhage from the puncture canals, we used additional balloon tamponade with a Linton or Sengstaken-Blakemore tube for 4 to 8 hours after sclerotisation.

2. Infiltration with epinephrine

Around bleeding gastroduodenal ulcers we infiltrated epinephrine solution diluted 1:5,000 with 2 to 3 ml per injection points in the direct vicinity of the ulcer's margin and then we treated the ulcer base with further infiltration or coagulated it with argon plasma in case of any remained oozing haemorrhage with reduced intensity.

3. Argon beam coagulation

We performed the treatments with ERBE Beamer One instrument connected to ERBE ACC 451 diathermic equipment. Coagulation current was dosed in "boluses" of 3 to 5 seconds, while paying attention to the suction of argon gas, particularly in the duodenum.

In addition to the procedures above, we had the opportunity to perform haemostasis in a patient with arterial haemorrhage from an ulcer base by using an endoscopic haemoclip on one occasion, and we used thermocoagulation with endoscopic diathermic head in 2 patients with oozing haemorrhage.

The endoscopic haemostasis was considered as successful when no rebleeding occurred within 24 hours.

During the evaluation we compared the results of examinations performed in organ transplant recipients with the results of urgent upper panendoscopies performed in non-transplant patients using the same principles and methods in both groups of patients.

In the second part of processing urgent examinations we looked for an answer to the question whether there was any difference between data of urgent endoscopies performed in kidney and liver recipients.

4. Statistical Analysis

Analysing our data, we registered patient number (n), mean and standard deviation (SD) for descriptive statistics and median value for the characterisation of time intervals. We used ANOVA test for the evaluation of parametric samples, and two-sample t test, chi square test and Fischer's exact test for examining differences between groups in non-parametric samples. For comparisons in case of relevance we also gave odds ratio (OR) with 95% confidence interval (CI). P values below 5% ($P<0.05$) were considered as significant.

Statistical analysis was performed with a software package Statistica 8.0 (*Statsoft*®).

Results

1. General Experiences of Upper Panendoscopies Performed in Organ Transplant Recipients

Regarding the 569 examined cases, the most common complaints and symptoms justifying endoscopy included upper abdominal pain (45.7%), overt or occult gastrointestinal haemorrhage (20.0%), and anaemia (18.1%). Also frequently seen were nausea/vomiting (17.9%), complaints of dyspepsia (15.3%), and weight loss (12.0%). This spectrum of signs and symptoms is similar to the complaints observed in non-transplant patient population and it essentially corresponds to those described in the literature.

As for endoscopic abnormities, we found no pathologic alteration in the upper segment of the gastrointestinal tract in 17.8% of the evaluated 561 examinations. Of the oesophageal lesions, reflux disease (23.5%) could be demonstrated with an incidence corresponding to that of the non-transplant population. As expected, the milder Los Angeles Stages A and B prevailed among our patients.

Candida infection, which is common in immunosuppressed patients, was seen in 47 of our patients (8.4%); this corresponds to the data of literature. The observed oesophageal ulcerations (3.9%) could be explained in part by reflux disease, in part by fungal oesophagitis. The relatively higher occurrence of oesophageal varicosity (6.8%) could be demonstrated mostly in recipients of liver transplantation.

Endoscopic gastritis, observed in a quarter of cases, was the commonest abnormity in the stomach. Also a high number of erosive gastritis (16%) was observed. Gastric ulcer was demonstrated in 47 patients; it was multiple in several patients and it was associated with duodenal ulcer as well.

With the exception of 1 adenoma, polyps found in the stomach were hyperplastic, and observed multiple in 2 of our patients. Relatively to the size of our patient population, the observed six gastric tumours

cannot be considered a high number. In a liver transplant recipient repeatedly recurring GIST tumour developed in the stomach, and it caused massive haemorrhages. The other gastric malignancies were observed in kidney recipients: 1 MALT lymphoma, 1 intestinal-type, well differentiated gastric adenocarcinoma at distal location, 1 sigillocellular cancer localised at the subcardial region, as well as gastric carcinoids in 2 patients.

Gastric retention due to a disorder of gastric emptying because of gastroparesis was found in 7 patients: in 4 cases it accompanied diabetes mellitus, and we succeeded in detecting CMV infection in further 2 cases.

Similarly to the stomach, endoscopic duodenitis was the commonest (17.1%) abnormity seen in the duodenum. Duodenal ulcers were observed relatively less frequently (5.4%) in comparison to gastric ulcers. We found 3 hyperplastic duodenal polyps: in 2 patients we demonstrated the rarely seen candidal duodenitis that was also confirmed by the microbiological examination (*Candida albicans*).

Endoscopic biopsy for histology and sample processing were performed in 88% of examined cases. Normal histological conditions were found in 10% of cases. We took samples from the oesophagus only when the endoscopic picture showed an abnormity. The observed cases of oesophagitis and oesophageal ulcers were mostly associated with reflux disease. Candidal infection was another common cause of oesophageal ulceration. We demonstrated Barrett's metaplasia in 5 patients and took them into care. The 2 oesophageal polyps, removed from the line of epithelial transition, were shown to be hyperplastic by histology.

During histological examination of gastric and duodenal samples chronic aspecific gastroduodenitis was seen most frequently (54.2%). In a quarter of examinations active gastritis was found, in association with Helicobacter pylori or CMV infections in several cases. By histological examinations, we demonstrated 11 gastric ulcers, 13 hyperplastic and 1 adenomatous polyp, and 6 malignant gastric tumours already detailed above.

Among abnormal findings in the duodenum, active duodenitis was the second most frequent (10.4%) behind chronic aspecific duodenitis. The 17% incidence of Helicobacter pylori lags significantly behind its 50 to 60% incidence in the general Hungarian population.

It seemed to be interesting to make a comparison between general data of endoscopies performed in kidney and liver recipients. In patients who underwent liver transplantation, endoscopic examinations were performed very much earlier (median: 1320 and 268 days for kidney and liver recipients respectively).

Of complaints justifying the examination, epigastric pain was the most frequent in both groups; it occurred in a considerably higher number of renal transplant recipients (47% vs. 31%). In this group of patients, endoscopy was significantly more often performed because of weight loss, in liver recipients upper gastrointestinal haemorrhage was clearly more frequent indication (29% vs. 18%).

Of the morphological endoscopic abnormalities, we found endoscopic gastritis with an incidence of >40% in both groups of patients. Reflux disease was demonstrated at a significantly higher rate among renal transplant recipients (26% vs. 8%). We observed more oesophageal varicosities during endoscopy of liver recipients (17% vs. 4%). According to our data candidal infections of the oesophagus are more frequent in renal transplant recipients (9% vs. 3%). In one sixth of examinations we found no abnormality in either group.

Comparing our histological findings, normal tissue structure was detected in 10% of cases. Most frequently, in half of kidney recipients and in two thirds of liver recipients, aspecific inflammation was found, that is difficult to interpret clinically. The rate of active gastritis was significantly higher among renal transplant recipients (27% vs. 12%) According to the result of the comparative investigation, Helicobacter pylori infection was scarce among liver recipients (3.5%), and the incidence of 18.5% demonstrated in kidney recipients was also significantly lower than the contamination observed in non-transplant patients.

2. Experiences of Diagnostics of Cytomegalovirus Infections of the Upper Gastrointestinal Tract

In biopsy samples during upper panendoscopies, we could identify significantly less CMV infections by light microscopic histological examination than by detection of CMV-DNA from the same samples (7.4% vs. 48%). **Therefore we used the detection of CMV-DNA for demonstrating the infection.**

We saw a substantial difference also in the number of samples, originating from the same case, in which we could confirm the infection by using PCR examination, viral DNA could be detected both in gastric and in duodenal samples in 71% of cases, while by light microscopic evaluation the infection was found to be proven in both localisations only in 22% of cases, this also indicates the limitations of the light microscopic method.

Evaluating the demographic data, no difference was found between CMV-infected and not infected patient populations. Similarly, no difference in the incidence of infection has been proven in relation to the fact if kidney or liver was the transplanted organ. The ratio of CMV infections was significantly higher in examinations performed between 31 and 90 days after transplantation. In our series of patients we could detect infections in the same proportion in case of any pre-transplant donor/recipient CMV serological status; there was no higher incidence of infections even in case of a positive donor/negative recipient constellation which meant the highest risk. We could detect CMV infection significantly more often in patients receiving tacrolimus immunosuppression (odds ratio 1.4).

We compared the clinical, endoscopic and histological picture of patients with upper gastrointestinal CMV infection with those who had no such infection. The clinical and endoscopic picture of the infected patients showed no relevant difference. As for the histological findings, there was a significantly higher ratio of active duodenitis/gastritis among infected patients.

Detection of *CMV infection* from the mucosa of the gastrointestinal tract in itself not necessarily possesses clinical significance. For establishing the diagnosis of gastrointestinal *CMV disease* the following criteria have to be fulfilled: (1) Characteristic signs and symptoms; (2) endoscopic morphological abnormalities, (3) histological alterations, (4) demonstration of viral presence; and (5) exclusion of other causes which could explain the signs and symptoms. Analysis of the listed criteria is a complex but important task, as the diagnosis of gastrointestinal CMV disease can be established, and antiviral therapy can be initiated on their base.

When evaluating the group of patients with CMV infection on the base of criteria listed in the previous paragraph and using the data available, we can state that gastrointestinal CMV disease was present in 126 patients (in 52.3% of detected infections). The diseases found are listed in an order of decreasing incidence as follows: CMV gastritis (45), CMV gastroduodenitis (19), CMV gastric ulcer (18), CMV oesophagitis (16), CMV oesophago-gastro-duodenitis (9), CMV duodenal ulcer (8), CMV duodenitis (7), and CMV gastric and duodenal ulcer (4).

Based on the diagnostic possibilities of our department, we defined when to recommend initiation of antiviral therapy in patients with proven or suspected gastrointestinal CMV infection/disease:

1. **Antiviral therapy should be started immediately** in the cases below:
1.1. Positive CMV antigenaemia, general symptoms, gastrointestinal complaints.
1.2. Positive CMV antigenaemia, gastrointestinal complaints, endoscopic findings may be typical to gastrointestinal CMV disease (deep oesophageal ulcers, multiple gastric or gastric and duodenal ulcers, etc.).

2. **Based on the histological findings** (which include detection of the virus by an appropriately sensitive and specific method), **antiviral therapy should be started immediately** in the case below:

Negative CMV antigenaemia, significant gastrointestinal complaints, more severe circumscribed or diffuse endoscopic alterations (severe erosive inflammation, ulceration), and infection can be detected from samples taken from them by biopsy, and also the histological examination indicates an active inflammation.

3. **Based on the histological findings** (which include detection of the virus by an appropriately sensitive and specific method**), antiviral therapy may be considered***:*
Negative CMV antigenaemia, significant or moderate gastrointestinal complaints, less severe endoscopic alterations (milder inflammatory abnormities), and active inflammation in samples taken by biopsy.

3. Comparative Evaluation of Urgent Upper Panendoscopies Performed in Organ Transplant Recipients

Analysis of demographic data in transplant recipients and non-transplant patients undergoing urgent endoscopic examination due to a haemorrhage showed the predominance of male patients in both groups (58.0% and 59.5% respectively). The examined transplant recipients were significantly younger with an average age of 49.6 years versus the 61.0 years of non-transplant patients. We found no difference between the two groups of patients in relation to the clinical course, individual sources and activity (Forrest stages) of the haemorrhage.

Endoscopic haemostasis was performed essentially at the same rate in both groups (34% and 37% in transplant recipients and non-transplant patients respectively); the used procedures were identical and the individual methods were applied at the same percentage. Endoscopic haemostasis was successful in 82% and 87% in transplant recipients and non-transplant patients respectively. Repeated urgent examinations were performed also in the same proportion. 9 transplant recipients and 13 non-transplant patients underwent emergency surgery because of upper gastrointestinal bleeding.

When compared kidney and liver recipients who underwent endoscopy because of a haemorrhage, we found no significant difference in the demographic data in relation to gender distribution (kidney: male 61% female 39%; liver: male 52%, female 48%) and average age (kidney 50.8 years, liver 47.8 years).
Urgent endoscopy was performed significantly more frequently in liver recipients (26% vs. 12%). There was no difference between the two groups of patients regarding the form of manifestation of bleeding. When compared the sources of bleeding, haemorrhages originating from an oesophageal varix rupture could be demonstrated only in liver recipients (29%); and we detected bleedings from gastric ulcers at a significantly higher rate in kidney recipient patients (24% vs. 9%).

For endoscopic haemostasis we used the above described procedures, with the same frequency. The rates of rebleedings (34% vs. 16%) and repeated urgent examinations performed because of a rebleeding (30% vs. 16%) were significantly higher in liver transplant recipients, and also endoscopic haemostasis was less successful (74% vs. 88%).

Conclusions

1. Experiences of Upper Panendoscopies Performed in Organ Transplant Recipients

1.1. We designed and applied an examination protocol for upper panendoscopy in transplant recipients and created a data base of the examination results.

1.2. We have come to the conclusion that recognition of typical pathologic conditions occurring in transplant recipient patients requires special experience in endoscopy and specific sample taking.

1.3. The 17% incidence of Helicobacter pylori infections in transplant recipients is significantly lower than the 49% observed in our non-transplant patients and the 50 to 60% seen in the general

Hungarian population. The rate of Helicobacter pylori infection was significantly lower in liver transplant patients; it was only 3.5% as compared to 18.5% in kidney recipients.

1.4. The incidence of reflux disease and candida oesophagitis is significantly higher in kidney recipients as compared to liver recipients.

2. Evaluation of the Diagnostics of Cytomegalovirus Infections

2.1. We analyzed the methods used for endoscopic diagnosis of CMV infection of upper gastrointestinal tract in organ transplant recipients and published them in an international journal.

2.2. We concluded and published that light microscopic histological examination alone is hardly suitable for detecting CMV infection of the upper gastrointestinal tract. We could demonstrate CMV infection with PCR technique sensitive and specific to viral DNA.

2.3. We concluded and published it in an international journal that there was a 48% rate of CMV infections of the gastroduodenal region in the population of transplant recipients examined.

2.4. Data of our patient population showed that CMV infection at the upper gastrointestinal tract occurred at the same rate in kidney and liver recipients; we could demonstrate no correlation between the infection and donor/recipient serostatus. We identified CMV infections in a significantly greater number among patients receiving tacrolimus-based immunosuppression. The incidence of infections was the highest at 30 to 90 days following organ transplantation.

2.5. The symptomatology as well as the endoscopic morphological and histological picture of upper gastrointestinal CMV infections is aspecific; the infection can be demonstrated by specific examinations of samples taken by endoscopic biopsy.

2.6. CMV infections detected at the upper gastrointestinal tract have clinical relevance only based on assessment of the entire clinical course.

2.7. We have formulated recommendations specifying the cases when antiviral treatment for CMV infection/disease is necessary.

3. Analysis of the Urgent Endoscopies

3.1. Comparing organ transplant recipients with non-transplant patients, we found no differences regarding the sources of bleeding and other characteristics of the haemorrhages.

3.2. Using identical procedures for endoscopic haemostasis; no differences were found in relation to rebleeding, success of haemostasis and patients undergoing surgery because of the bleeding.

3.3. We found a clearly higher rate of urgent examinations performed because of haemorrhage in liver recipients as compared to kidney recipients: the most frequent source of haemorrhage was oesophageal varix rupture. In this group endoscopic haemostasis was less successful, the rebleeding rate was more frequent and the number of repeated endoscopies due to recurrent haemorrhage was also higher.

3.4. We observed haemorrhages originating from gastric ulcers more frequently in kidney recipients, and the rate of bleedings originating from duodenal ulcers as well as erosions was also higher.

List of Publications

Publications connected to the PhD thesis

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