High frequency of ulcers, not associated with Helicobacter pylori, in the stomach in the first year after kidney transplantation

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Abstract

Background. Although gastrointestinal (GI) symptoms are very frequent in organ transplant patients, there is a paucity of data about the endoscopic findings of kidney recipients.

Methods. Two thousand one hundred and thirty-five kidney transplants were performed between 1994 and 2007. During that period, 672 gastroscopies were performed in 543 of those patients. Their mean age was 49.5 years and 56.9% were male. Immunosuppressive combinations included cyclosporine–mycophenolate–steroids, cyclosporine–steroids and tacrolimus–mycophenolate mofetil–steroids. Ninety-eight percent of the patients received acid suppression therapy.

Results. The rate of clinically significant endoscopic findings was 84%. Macroscopic findings included inflammation in 46.7%, oesophagitis in 24.7%, ulcer in 16.9% and erosions in 14.8% of cases. Twenty-nine percent of endoscopies showed ulcer disease more frequently in the first 3 months (P = 0.0014) after transplantation than later, and 45.7% of all ulcers developed in the first year. The presence of Helicobacter pylori was verified in 20.9% of cases, less than in the general, and also in the uraemic population (P < 0.0001). There was no association between the presence of H. pylori and ulcers (P = 0.28). Steroid pulse treatment for rejection was not associated with more ulcers (P = 0.11); the use of mycophenolate mofetil increased the risk of erosions by 1.8-fold.

Conclusion. More than 25% of all kidney recipients required upper endoscopy in their ‘post-transplant life’; the prevalence of ‘positive findings’ and ulcer disease was higher than in the general population (P < 0.0001). The most vulnerable period is the first 3 months. Mycophenolate mofetil had an impact on GI complications, whilst the presence of H. pylori in the transplant population is not associated with the presence of ulcers.

Keywords: endoscopy; Helicobacter pylori; kidney transplantation; ulcer disease; upper gastrointestinal tract

Introduction

Upper gastrointestinal (GI) symptoms are frequent in organ transplant recipients. Peptic ulcers and related pathologies such as gastritis and duodenitis are known to occur with increased frequency (20–60%) and severity in renal transplant recipients. The frequency of severe complications is about 10% among transplant recipients and 10% of those might prove fatal [1–5]. Compared to the general population, renal transplant recipients have an age-adjusted ratio for GI bleeding of 10.69 at 1 year of follow-up [6]. Frequency of ulcer disease was proven to be 8.3–10.7% of endoscopically examined general gastroenterology patients [7,8]. Similar data among transplant patients are not available. GI complications might play a role in the outcome of kidney transplantation, as they are associated with an increased risk of graft loss, since dose reduction or even withdrawal of immunosuppressive (IS) agents might be necessary [3, 9–11]. Different factors can cause GI symptoms: surgical stress, the operation itself, local irritant and pro-inflammatory effects of IS and/or other drugs, the numerous pills some patients have to take every day and bacterial, viral and mycotic infections [12,13]. The GI tract accounts for a large component of non-allograft-related complications seen after all types of solid organ transplantation [14]. Whilst endoscopic alterations of liver transplant recipients are the focus of numerous studies [15–18], only few studies have been done on the endoscopic findings of renal patients and include only small numbers [19,20].

By summarizing and analysing the largest endoscopic database in the literature, our aim was to ascertain the frequency and the time of occurrence of ulcer disease after kidney transplantation.

Materials and methods

Patients

From January 1994 to December 2007, 2143 kidney transplants were performed in a large transplant centre. Six hundred and seventy-two upper GI
endoscopies were done in 543 kidney transplant patients (25.3% of recipients). Patients with GI complaints following informed written consent, underwent an upper endoscopy examination; 56.9% of them were male, with a mean age of 49.5 ± 12.8. All patients received an acid-blocker as ulcer prophylaxis. Data of kidney transplant patients were collected for this cross-sectional (date of endoscopy), descriptive study.

**Endoscopy**

Two senior surgeon-gastroenterologists performed all the endoscopic examinations esophageo-gastro-duodenoscopy = gastroscope (EGD). The upper GI tract was examined. The endoscopic abnormalities were evaluated according to international standards [21–25]. Forceps mucosal biopsies were taken from a specific lesion (e.g. ulcer) if present and from every patient from the first part of the duodenum, the gastric antrum and the gastric corpus (2-2 biopsy samples from each localization). Biopsy samples were investigated by conventional histology for mucosal changes (haematoxylin–eosin and Giemsa). Patients were considered as *Helicobacter pylori (Hp)* positive, if histology proved its presence. No biopsy was taken in cases of bleeding, in patients with known coagulation disorders or those on anticoagulant therapy (except aspirin).

**Immunosuppression and acid suppressive therapy**

The IS medication used at the time of endoscopy was collected and analysed. Cyclosporine (CSA), tacrolimus (TAC), mycophenolate mofetil (MMF) and steroids (ST) were used in various combinations for maintenance therapy. ST were administered in a tapering dose once a day. CSA, MMF or methylprednisolone was used as ST. At the time of EGD, the initial dose of MMF was 2 × 1 g, according to an established protocol. TAC and MMF were administered twice daily. Target trough levels of CSA and TAC were 7–10 ng/mL at the long term. Prednisolone or methylprednisolone was used as ST. The initial dose of MMF was 2 × 1 g, according to an established protocol. Auramine–methylprednisolone was used as ST. At the time of endoscopy, the most frequently used (75.1%) IS combinations were CSA–MMF or MMF–ST triple treatment, CSA–ST double treatment and TAC–MMF–ST triple therapy. All other combinations occurred in <5% in that material, and these were excluded from the IS-related analysis. A total of 34.51% of all transplant recipients and 34.56% of endoscopically examined patients received intravenous ST pulse therapy. Out of the latter ones, 15.53% received it in the 3 months period prior to the endoscopy.

Data of acid suppressive therapy (AST) ‘before’ endoscopy were also collected and analysed. Nearly all (97.8%) patients received AST. Out of them, 56.1% received a histamine receptor antagonist (H2RA) and 43.8% a proton pump inhibitor (PPI). There was a variable usage of PPIs and H2 receptor antagonists; however, the general use did not change during the study period. There was no difference between the IS groups according to AST treatment received, P = 0.33.

**Statistical analysis**

Qualitative data were analysed by Fisher’s exact test or with chi-square test with a two-sided probability value. Continuous variables were compared using the Mann–Whitney U or Kruskal–Wallis test. Frequencies of specific pathologic phenomena were calculated by direct counting. The influence of risk factors was quantified using odds ratio (OR). P-values of below 0.05 were considered significant. Statistics were performed using STATISTICA (data analysis software system; StatSoft, Inc., 2008, version 8.0, www.statsoft.com).

**Results**

**Macroscopic findings**

Only 16.2% of the patients examined had the absence of any abnormal endoscopic findings. The most frequent abnormality found were inflammatory changes, with almost one-half of the patients showing signs of gastritis and/or duodenitis. Oesophagitis, varices, duodenal and/or gastric ulcer disease, erosions, oesophageal varices and polypoid lesions were frequently observed findings. Their frequency was independent from renal function assessed by serum-creatinine level (Table 1). Fifty-two out of 92 ulcer patients (56.5%) had gastric, 33 (35.8%) duodenal and 7 (7.6%) both kinds of ulcer. In five cases, malignant tumour was suspected during the endoscopy with three of them histologically proven: one of those was mucosa associated lymphoid tissue (MALT) lymphoma, the others were adenocarcinomas. Altogether six malignant tumours were found, in the other three cases, previously a diagnosis of polyp or ulcer was made. Other rare abnormalities seen were diverticula, vascular angiectasia (suspicious for Kaposi-sarcoma) and Mallory–Weiss syndrome.

**Table 1.** Most frequent macroscopic lesions, creatinine medians (μmol/L), rate of *H. pylori* and their relationship

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Frequency</th>
<th>Rate of <em>H. pylori</em> positivity</th>
<th>P</th>
<th>Serum creatinine, if the lesion is</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Present</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not present</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>46.7%</td>
<td>22.2%</td>
<td>0.57</td>
<td>147</td>
<td>0.45</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>24.9%</td>
<td>19.8%</td>
<td>0.80</td>
<td>128</td>
<td>0.95</td>
</tr>
<tr>
<td>Ulcer</td>
<td>16.9%</td>
<td>26%</td>
<td>0.28</td>
<td>120</td>
<td>0.19</td>
</tr>
<tr>
<td>Erosions</td>
<td>14.8%</td>
<td>16.7%</td>
<td>0.41</td>
<td>150</td>
<td>0.24</td>
</tr>
<tr>
<td>Varices</td>
<td>3.8%</td>
<td>20.8%</td>
<td>0.58</td>
<td>176</td>
<td>0.22</td>
</tr>
<tr>
<td>Polypoid lesions</td>
<td>2.9%</td>
<td>20.9%</td>
<td>0.75</td>
<td>150</td>
<td>0.81</td>
</tr>
<tr>
<td>Negative</td>
<td>16.2%</td>
<td>21.9%</td>
<td>0.36</td>
<td>130</td>
<td>0.20</td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td>20.9%</td>
<td>20.9%</td>
<td>0.85</td>
<td>140</td>
<td></td>
</tr>
</tbody>
</table>

In 62 (11.4%) cases, the *H. pylori* status was not determined. These examinations were mainly repeated or acute endoscopies for bleeding. Out of the 481 histologically examined, the presence of *H. pylori* was verified in 101 cases, representing 20.9%. For a two-year period during the study we performed histology and rapid urease test (RUT) in parallel. Whilst the specificity of RUT was 98.5%, its sensitivity was only 38.5%, so we stopped performing it in 2004. There was no difference according to gender or age (Table 2).

The presence of *H. pylori* was not associated with the presence of peptic ulcer: 20 of 101 *H. pylori*-positive patients as compared to 57 of 380 *H. pylori*-negative patients had ulcers (P = 0.28). Vice versa: 26% of ulcer patients were positive for *H. pylori*. There were no significant associations between positivity for *H. pylori* and erosions, oeso-
High frequency of ulcers not associated with *H. pylori* in the stomach

Table 2. Demographic data according *H. pylori*

<table>
<thead>
<tr>
<th></th>
<th><em>H. pylori</em> pos.</th>
<th><em>H. pylori</em> neg.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (56.55%)</td>
<td>20.96%</td>
<td>79.04%</td>
<td>P = 1.0</td>
</tr>
<tr>
<td>Female (43.45%)</td>
<td>21.05%</td>
<td>78.95%</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>50.54</td>
<td>49.24</td>
<td>0.53</td>
</tr>
</tbody>
</table>

phagitis, macroscopic signs of inflammation, metaplasia or atrophy (Table 1).

**Impact of IS agents**

We compared the main groups according to the observed diagnosis and infection rate. There were no differences in the incidence of negative findings, inflammation, ulcer and oesophagitis and the presence of *H. pylori*. However, there were differences in the incidence of erosive lesions; both the differences between the groups and the trend (P = 0.01) are significant (Table 3). This table displays the rate of the particular lesions of those receiving ST pulse every three months prior to endoscopy as well. Out of them, 18.75% had an ulcer (P = 0.106). MMF was proven as an independent risk factor for erosive lesions, OR: 1.83 (1.02–3.29, P = 0.043) when correcting for the presence of other risk factors.

**Impact of acid suppression therapy**

We compared the H2RA and PPI groups according to the indications, observed diagnoses and infections. These groups did not differ in their nature of presenting complaints: pain, dyspepsia, anaemia and bleeding occurred at the same rate. Respective P-values were 0.9, 0.55, 0.16 and 0.86. There was no difference in the incidence of inflammation (P = 1.0), oesophagitis (P = 0.68), erosions (P = 0.60), ulcers (P = 0.20) or negative findings (P = 0.87) depending on the AST given, and there was no difference in mycosis (P = 0.16). The only significant difference was in the presence of *H. pylori*; it was present in 22.6% of patients who received H2RA and in 12.4% of those who received PPI (P = 0.044).

**Timing of endoscopy**

The time between transplantation and endoscopy varies from 3 days up to almost 19 years, median was 3.39 years. However, 29% (157) of the patients were examined in the first post-transplant year, and 58.5% (92) of them, which is 16.9% of all, in the first 3 months, as shown in Figure 1. Ulcers were more commonly found in patients requiring earlier endoscopy: 1.65 vs 3.66 years for patients where no ulcer was found (P = 0.009). The frequency of ulcer disease was 29.3% of the examinations in the first 3 months, 26.3% in the first year and only 12.9% later on, P = 0.0014. Twenty-seven (29.3%) out of 92 ulcers developed in the first 3 months, forty-two (45.7%) in the first year and all the others at a constant rate later on (Figure 2). The *H. pylori* positivity rate on examination decreased with time after transplantation, but this was statistically non-significant.

**Discussion**

This is the largest series, to our knowledge, of endoscopic findings in consecutive kidney transplant patients scoped for a specific indication. Endoscopy is not part of the routine pre- or postoperative schedule in this unit. By nature, this examination is relatively unpleasant, invasive and expensive, with a small but existing hazard of perforation of about 0.06% [26].

We included only endoscopies performed in our centre on those patients to guarantee homogeneity. The way of follow-up in our centre, though, means that only few endoscopies (perhaps <5%) were performed elsewhere. According to our study, at least 25% of all patients require upper endoscopy in their ‘post-transplant life’. We did not find data to compare this rate.

Endoscopy was completely negative in about 16% of our cases, which reflects other reports [20]. This rate (84%) of clinically significant endoscopic findings is much higher than expected from data of general gastroenterology patients, where this figure is around 58% [7,27].

The most important period for upper GI symptoms requiring endoscopy was the first year and particularly the first 3 months. Almost one-third of the patients were investigated in the first year. The importance of the first year was observed in other reports as well, where 51% of the verified GI complications occurred during that time [5]. In the first 3 months 29%, and in the first year 26% of the endoscopic examinations revealed an ulcer disease. Out of 92 ulcers, 29% developed in the first 3 months and 45.7% in the first post-transplant year. The nearly 17% incidence of well-defined ulcer disease is significantly (P < 0.0001) higher comparing it with gastroenterology patients undergoing endoscopy [7,8]. The risk of ulcer disease is 1.69-fold (1.32–2.15 confidence interval (CI) 95%) for a kidney recipient. There are no similar data for the prevalence of ulcers in transplant patients in the literature. The true prevalence of ulcer disease might be even higher, as a large proportion of patients do not experience symptoms [28].

Table 3. GI lesions and their frequency according to the IS regimen and steroid pulse therapy

<table>
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<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>12.0%</td>
<td>13.9%</td>
<td>17.9%</td>
<td>0.53</td>
<td>25.0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Inflammation</td>
<td>51.0%</td>
<td>50.5%</td>
<td>38.5%</td>
<td>0.15</td>
<td>31.23%</td>
<td>0.18</td>
</tr>
<tr>
<td>Ulcer</td>
<td>19.0%</td>
<td>16.1%</td>
<td>15.4%</td>
<td>0.77</td>
<td>18.8%</td>
<td>0.11</td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td>24.7%</td>
<td>23.9%</td>
<td>17.3%</td>
<td>0.45</td>
<td>7.1%</td>
<td>0.18</td>
</tr>
<tr>
<td>Erosions</td>
<td>15.9%</td>
<td>18.4%</td>
<td>24.4%</td>
<td>0.03</td>
<td>31.2%</td>
<td>0.0547</td>
</tr>
</tbody>
</table>
The individual IS drugs and combinations received seemed to have a significant impact on the patient’s GI status. MMF was proven to increase the risk of erosions of the gastro-duodenal mucosa 1.83-fold (1.02–3.29 CI 95%). Patients receiving the TAC–MMF–ST regimen had the highest frequency of erosive lesions. The effect of corticosteroids is still controversial; high doses are suspected to be ulcerogenic, but real evidence is not available [12,29–31]. ST treatment can mask the symptoms and delay treatment [32]. In our series, even high-dose intravenous ST pulse therapy for rejection was not associated with GI lesions observed endoscopically.

Administration of AST for ulcer prophylaxis is common at most transplant centres [1,12,33,34]. The specific drug used in our centre was dependent on availability, price etc. and not only on medical grounds. The rate of observed endoscopic alterations did not differ in the H2RA and in the PPI group, indicating the equivalence of these two groups of AST in this setting. The only difference was in the presence of H. pylori; PPIs facilitated the eradication ‘by chance’ more efficiently than they do in the general population.

Over the last 20 years there has been considerable interest in the role of H. pylori in the pathogenesis of gastritis and peptic ulceration in the general population [35]. Data reported on the prevalence of Helicobacter pylori among transplant recipients are contradictory. There are only a few studies reporting endoscopic results of transplant pa-
High frequency of ulcers not associated with *H. pylori* in the stomach

tients [2,36–38], and there are some more reporting of *H. pylori* serologic examinations [39–41]. Published data vary from 29 to 70%. Seroprevalence of *H. pylori* is 49% in a large Hungarian uremic cohort [42]. In our endoscopic unit experience, 47% *H. pylori* positivity rate was detected with biopsy in general gastroenterology patients during the same period (data not published). The observed 20.9% frequency of biopsy-proven *H. pylori* infections in our study represented a highly significant difference (P < 0.0001).

Our results demonstrated a high, ‘spontaneous’ eradication rate in transplanted patients. The rate of *H. pylori* did not change in time in our present material, and the age of positivity and negativity was the same. These results suggest that eradication happens at the very early peri-operative period, when prophylactic antibiotics and AST are given together. The presence of *H. pylori* did not result in significant postoperative gastric complications. Due to the constant use of AST, the sensitivity of RUT was only 38.5%. As a result, we do not recommend it in this particular group of patients. As both *Helicobacter pylori* [43] and immunosuppression have been linked to an increased risk of developing malignancy, we considered our patients as ‘high-risk patients’, and a ‘test and treat’ strategy was followed. The Maastricht Consensus Reports were used as basis for the eradication protocol [44].

In the general population, only 15% of *H. pylori*-infected persons develop peptic ulcer disease, suggesting that specific factors are required for ulceration to occur [45]. Less than one-third (26%) of gastric ulcer patients were *H. pylori* positive and even less (17%) were positive among patients found to have a duodenal ulcer. Neither the type of IS drugs nor the presence of *H. pylori* had a statistically significant impact on ulceration. This finding suggests that ulceration in transplant recipients is a multifactorial process that may involve the interaction of acid secretion, *H. pylori*, IS agents and other medications rather than a single factor.

Specific IS drugs, opportunistic infections and other clinical circumstances that affect transplant patients are not seen frequently in the general practice of gastroenterology. Thus, the endoscopist at a transplant centre has to be able to recognize, identify and treat the unique problems seen in a transplant population. Giving prophylactic acid secretion blockers, minimizing the number of pills a patient has to take a day and adopting a low threshold for endoscopy are among the most important measures that could be used to avoid GI complications after transplantation [46].

Conflict of interest statement. None declared.

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Barriers to living kidney donation identified by eligible candidates with end-stage renal disease

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Abstract

Background. Among eligible transplant candidates with end-stage renal disease, only a minority receive a living donor kidney transplant (LDKT), suggesting that there are barriers to receipt of this optimal therapy.

Methods. A validated questionnaire was administered to adults active on the deceased donor transplant waiting list, identified from the Southern Alberta Renal Program database. The questionnaire included both quantitative and qualitative items addressing issues related to LDKT in the categories of knowledge, opportunity, fear and guilt.

Results. Of the 196 subjects invited to complete the questionnaire, 145 (74%) responded. Not knowing how to ask someone for their kidney was the most frequently reported barrier, identified by 71% of respondents. Those that stated that living donation did not pose significant long-term health risks to the donor [odds ratio (OR) = 3.40, 95% CI 1.17–9.46, P = 0.01] and those who understood how and