Early gastric post-transplantation lymphoproliferative disorder and *H pylori* detection after kidney transplantation: A case report and review of the literature

CL Nash MD¹, LM Price FRCPC¹, DA Stewart FRCPC², F Sepandj FRCPC³, S Yilmaz PhD MD⁴, A Barama MD⁴

CL Nash, LM Price, DA Stewart, F Sepandj, S Yilmaz, A Barama. Early gastric post-transplantation lymphoproliferative disorder and *H pylori* detection after kidney transplantation: A case report and review of the literature. *Can J Gastroenterol* 2000;14(8):721-724. The incidence of post-transplantation lymphoproliferative disorder (PTLD) in the adult renal transplant population ranges from 0.7% to 4%. The majority of cases involve a single site and arise, on average, seven months after transplantation. Histopathology usually reveals B-cell proliferative disease and has been standardized into its own classification. Treatment modalities consist of decreased immunosuppression, eradication of Epstein-Barr virus, surgical resection, systemic chemotherapy and monoclonal antibody therapy; however, mortality remains high, typically with a short survival time. In patients who have undergone renal transplantation, approximately 10% of those with PTLDs present with gastrointestinal symptomatology and disease. Reported sites include the stomach, and small and large bowel. Very few cases of *Helicobacter pylori* or mucosal-associated lymphoid tissue have been described in association with PTLD. In the era of cyclosporine immunosuppression, the incidence of PTLD affecting the gastrointestinal tract may be increasing in comparison with the incidence seen with the use of older immunosuppression regimens. A case of antral PTLD and *H pylori* infection occurring three months after renal transplantation is presented, and the natural history and management of gastric PTLD are reviewed.

Key Words: Epstein-Barr virus; Gastric lymphoma; Immunosuppression; Kidney transplantation; Post-transplantation lymphoproliferative disease

Anomalie gastrique lymphoproliférative post-transplantation précoce et dépistage de *H. pylori* après la transplantation rénale : rapport de cas et revue de la littérature

RÉSUMÉ : La prévalence de la maladie lymphoproliférative suivant la transplantation chez les adultes qui subissent une greffe rénale varie de 0,7 à 4 %. Dans la majorité des cas, un seul site est atteint et apparaît en moyenne sept mois après la transplantation. L'histopathologie révèle habituellement une maladie proliférative affectant les lymphocytes B et a été standardisée en une classification qui lui est propre. Les modalités thérapeutiques reposent sur un traitement immunosuppresseur de base, sur l'éradication du virus Epstein-Barr, la résection chirurgicale, la chimiothérapie systémique et le traitement par anticorps monoclonaux. Par contre, la mortalité reste élevée avec un temps de survie en général bref. Chez les patients qui ont subi une greffe rénale, environ 10 % de ceux qui développent une maladie lymphoproliférative présentent des symptômes de maladies digestives. Parmi les sites affectés, mentionnons l'estomac, le grêle et le côlon. Aucun cas d'*Helicobacter pylori* ou de maladie des tissus lymphoïdes muqueux n'a été décelé en association avec la maladie lymphoproliférative. Avec l'immunosuppression à la cyclosporine, l'incidence de la maladie lymphoproliférative affectant les voies digestives peut être à la hausse comparativement à l'incidence que l'on observe avec d'autres schémas immunosuppresseurs plus anciens. Un cas de maladie lymphoproliférative et d'infection à *H. pylori* antrales survenu trois mois après une greffe rénale est présenté ici, de même qu'un survol de l'histoire naturelle et de la prise en charge de la maladie lymphoproliférative gastrique.

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Departments of ¹Gastroenterology, ²oncology and ³Nephrology, and ⁴Division of Transplantation Surgery, University of Calgary, Calgary, Alberta
Correspondence and reprints: Dr LM Price, 711 South Tower, 3031 Hospital Drive NW, Calgary, Alberta T2N 2T9. Telephone 403-283-6613, fax 403-270-7722

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Post-transplantation lymphoproliferative disorder (PTLD) was first described by Penn et al (1) in 1969. Risks of developing PTLD relate to the degree of immunosuppression after solid organ transplantation and infection with Epstein-Barr virus (EBV) (2). PTLD is found at one site, most commonly the allograft, in 65% of patients who have undergone renal transplantation. Other sites (in order of prevalence) include the lymph nodes, liver, lung, mediastinum, intestine, central nervous system (CNS) and skin. EBV has been implicated in approximately 70% of cases (2-4).

Treatments for post-transplantation lymphoma of the gastrointestinal tract are not specific but are the treatments used for any post-transplant lymphoma. These tumours are typically aggressive. We describe a patient who presented three months after renal transplantation with a high grade B-cell lymphoma of the antrum.

CASE PRESENTATION

A 49-year-old man presented 87 days after cadaveric renal transplantation with an eight-day history of epigastric pain immediately upon swallowing, lasting up to 1 h. He had no symptoms of fevers, chill, cough, weight loss, sweats, anorexia, early satiety or lymphadenopathy. His medical history was significant for a renal transplant in April 1999, 15 years after the diagnosis of focal glomerular sclerosis. The post-transplant course was complicated by hypertension and prednisone-induced glucose intolerance. The renal graft functioned well, and immunosuppression therapy consisted of cyclosporine (150 mg bid), prednisone (12.5 mg/day) and mycophenolate (500 mg bid). There was no history of non-steroidal anti-inflammatory drug ingestion.

Physical examination revealed normal vital signs. Results of head, neck and cardiopulmonary examinations were unremarkable. No lymphadenopathy was present. The abdominal examination revealed mild epigastric tenderness and the palpable transplanted kidney in the right lower quadrant. Gastroscopy performed 48 h later showed multiple (more than 10) large, deep antral ulcerations with raised erythematous borders (Figure 1, top). Histopathology confirmed diffuse, large B-cell lymphoma in the lamina propria, with gland preservation and small infiltrates of reactive T cells (Figure 1, bottom). Histopathology confirmed the presence of *Helicobacter pylori*, and EBV was detected by polymerase chain reaction analysis. Results of computed tomography of the abdomen and pelvis; upper gastrointestinal series and small bowel follow-through; chest x-ray; and bone marrow aspirate were normal.

H pylori was treated for seven days with lansoprazole (Prevacid; Abbott, Canada), amoxicillin trihydrate (Amoxil; Wyeth-Ayerst, Canada) and clarithromycin. EBV was treated with acyclovir. Immunosuppression was altered; the cyclosporine dosage was decreased to 75 mg/day, the prednisone dosage was kept at 12.5 mg/day and mycophenolate was discontinued. Because of the grade of lymphoma and severity of symptoms, the patient was treated on an urgent basis with chemotherapy, receiving cyclophosphamide 1200 mg,

Figure 1) Top Gastric antrum. Multiple large ulcerations isolated in the antrum of a 49-year-old patient 89 days after cadaveric renal transplantation. **Bottom** Histopathology (hematoxylin and eosin stain) of antral biopsies showing high grade B-cell lymphoma. *Helicobacter pylori* was present but is not shown on this slide. The patient was positive for Epstein-Barr virus by polymerase chain reaction

doxorubicin hydrochloride (Adriamycin; Pharmacia & Upjohn, Canada) 82 mg, vincristine 2 mg for one day and prednisone 100 mg/day for five days. His symptoms resolved on day 4 after chemotherapy.

Repeat gastroscopy 54 days after chemotherapy revealed persistent but markedly improved superficial antral ulcerations (Figure 2). Histopathology showed mild, chronic inflammation of the lamina propria, with no malignant cells. *H pylori* was not detected, but cells suggestive of cytomegalovirus infection were present. The patient underwent three days of intravenous ganciclovir treatment, followed by five further cycles of chemotherapy. One-hundred and thirty days

Figure 2) Repeat gastroscopy 54 days after chemotherapy. The patient had mild, persistent antral gastritis, but showed marked improvement. Pathology was negative for lymphoma and *Helicobacter pylori*

Figure 3) Follow-up gastroscopy 130 days after chemotherapy. The mucosa was normal, and biopsy results were negative for lymphoma

after chemotherapy was initiated, gastroscopy revealed normal mucosa and no evidence of tumour recurrence (Figure 3).

DISCUSSION

Immunosuppression after solid organ transplantation results in a 100-fold increased rate of malignancy; lymphoma is the second most common type of malignancy, comprising 20% of all malignancies. In patients who have undergone renal transplantation, the incidence of PTLD disease is approximately 1%. The most common site of involvement is the renal allograft, followed by the lymph nodes, liver, lung and mediastinum, intestine, CNS and skin (2,4). Gastrointestinal PTLD is most common in patients who have undergone renal transplantation compared with those who have undergone other solid organ transplantations. This feature of different organ involvement among distinct populations of transplant recipients is not understood (5).

Approximately 10% of PTLD in renal transplant recipients presents as gastrointestinal symptoms, most notably fever, pain and perforation. Most cases affect the small and large intestines, whereas few cases of isolated gastric PTLD have been reported (6). Among transplant recipients who develop PTLD, a variety of clinical presentations are apparent. Some, notably young patients (mean age 23 years), present early in the post-transplant course (less than one year) with an acute infectious mononucleosis-like illness of fever, pharyngitis and lymphadenopathy. A second group presents with mass-like extranodal disease. This group is characteristically older (mean age 47 years), presents later

after transplantation and often has a more aggressive course (2).

The pathogenesis of PTLD is most commonly thought to depend on the degree of immunosuppression and EBV infection. Although the intensity of immunosuppression is certainly implicated in the development of PTLD, the use of cyclosporine in the 1980s led to a dramatic change in organ involvement. Before the use of cyclosporine, CNS PTLD was prevalent. Since the widespread introduction of cyclosporine, CNS lymphoma has significantly declined, and non-Hodgkin lymphoma (NHL) has increased from 12% in noncyclosporine regimens to 30% in cyclosporine regimens (5). Malignancy increased with the initiation of cyclosporine treatment but has returned to baseline levels with the use of lower doses of immunosuppression (7). There are not enough data regarding gastrointestinal PTLD to know whether its specific incidence has increased, but with the overall elevated rate of NHL, an increase may be expected, predominantly in renal transplant recipients (8).

Surveys of renal transplant recipients on active immunosuppression have shown a high prevalence of *H pylori* colonization, but the results are inconclusive regarding the degree of pathogenicity. One survey of 29 renal allograft patients revealed that, despite an *H pylori* prevalence of 60% to 80%, active gastritis was present in only 7% (9). Another study of 33 renal transplant recipients found an *H pylori* prevalence of nearly 50%, with a strong correlation with symptomatic dyspepsia and ulceration. No relation was found between colonization and prednisolone dose or cyclosporine levels (10). Very few cases of mucosa-associated lymphoid tissue

(MALT) have been described in immunosuppressed populations. Wotherspoon et al (11) reported three cases of MALTomas with documented *H pylori* infection in two patients on antirejection therapy and one patient with acquired immunodeficiency syndrome. Hsi et al (12) reported five MALT-type lymphomas in transplant patients. Each case demonstrated classic, low grade, gastric B-cell lymphoma, with associated *H pylori*. No EBV was found in these cases.

Treatment of gastrointestinal-related PTLT is not unique among PTLT treatments, but its prognosis may be. Hanto et al (3) suggested that patients presenting with local masses (as opposed to a mononucleosis-like illness) are more likely to have a monoclonal lymphoma histology, which is generally more aggressive than polyclonal hyperplasia or lymphoma. Therefore, EBV treatment and a reduction in immunosuppression, while effective in isolated cases, are usually inadequate. Isolated gastrointestinal PTLT has been successfully resected (13). Systemic treatment with chemotherapy and monoclonal antibodies is often used (14). The effectiveness of therapies cannot be compared directly because of the small number of cases in each review. Unfortunately, mortality remains high overall, with an estimated survival of six months. Some studies have reported that gastrointestinal involvement results in an aggressive course (2,5), while others suggest that it may be a positive predictor;

Nalesnik et al (6) reported that 10 of 12 cases survived from 20 to 88 months.

In the case presented, eradication of *H pylori*, and reduction in immunosuppression and antiviral treatment did not improve symptoms. As a result of the high grade nature of the lymphoma and the severity of our patient's symptoms, early intervention with systemic chemotherapy was initiated. To date (12 months after diagnosis), the patient has responded rapidly and completely to systemic chemotherapy. Surprisingly, all evidence of lymphoma was cleared after one round of chemotherapy, as proved by repeated biopsies, which were negative for PTLT.

CONCLUSIONS

Further databases need to be gathered regarding PTLT, its clinical course and its outcome to treatment, particularly as new, more potent immunosuppressive chemotherapies become available and used widely. As one of the most devastating consequences of transplantation, this area should continue to be investigated. Furthermore, although PTLT is not a common disease within the scope of gastroenterology, it should be considered in transplant recipients presenting with gastrointestinal symptoms.

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