PNEUMATOSIS INTESTINALIS IN PATIENTS AFTER CADAVERIC KIDNEY TRANSPLANTATION: POSSIBLE RELATIONSHIP WITH AN ACTIVE CYTOMEGALOVIRUS INFECTION

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Summary

Four patients are presented with pneumatosis intestinalis following kidney transplantation, all with severe cytomegalovirus (CMV) infection. Two patients had a primary infection and two patients had CMV reactivation. One patient died because of disseminated CMV infection. Two patients had concomitantly an active, non-obstructive duodenal ulcer. In a control population of 17 patients who suffered from a duodenal ulcer post-transplant without any evidence of CMV infection, we could not demonstrate pneumatosis intestinalis. We suggest a possible relationship between pneumatosis intestinalis and active CMV infection. The possible mechanisms responsible for this relationship are discussed.

Introduction

Gastrointestinal complications after cadaveric renal transplantation are numerous and include oesophagitis, ulcers with or without haemorrhage or perforation, pancreatitis and infarction [1,2]. These complications are believed to be related to the use of immunosuppressive drugs, especially corticosteroids [1,2]. Pneumatosis intestinalis is an uncommon disease whose pathogenesis is still obscure. Reports of pneumatosis intestinalis in patients with a kidney transplant are rare and are also believed to be related to the use of immunosuppressive drugs [1]. We recently observed two patients with cadaveric kidney transplants and pneumatosis intestinalis. Both patients had active CMV infection. The association prompted us to look retrospectively at our transplant patient population to see whether we could find other patients with pneumatosis intestinalis in combination with an active CMV infection.

Patients and methods

In 1982 we identified two patients who suffered from pneumatosis intestinalis. Retrospectively we found two other patients with this abnormality in our
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age/Sex</th>
<th>Type of CMV-infection</th>
<th>Gastrointestinal symptoms before transplantation</th>
<th>Symptoms moment of pneumatosis</th>
<th>Diagnosis pneumatosis weeks after transplantation</th>
<th>Roentgen</th>
<th>Pneumoperitoneum</th>
<th>Concomitant ulcer</th>
<th>Final outcome</th>
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<tr>
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<td>47/F</td>
<td>primary</td>
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<td>–</td>
<td>yes (UD)</td>
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</tr>
<tr>
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<td>react.</td>
<td>none</td>
<td>yes, aspecific</td>
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<td>none</td>
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</table>
transplant population. Patient data are given in Table I. All four patients had received a cadaveric kidney transplant and were treated with standard immunosuppression consisting of azathioprine and corticosteroids only. All four patients had active CMV infection with fever, arthralgia, leucopenia, liver function abnormalities and changes in CMV-serology, when pneumatosis was detected.

The diagnosis of pneumatosis was made on plain X-ray of the abdomen with the patient in the supine position, at which time intramural gas was present [3]. The serological diagnosis of active CMV infection was defined as a threefold or greater rise in titres of complement fixing antibodies (CFA) against CMV or a fourfold or greater rise in antibodies to CMV early (EA) and late (LA) antigens [4]. The patients were considered to be seronegative for CMV when the CFA titres were less than 1:4 and the titres of antibodies to CMV-EA and -LA less than 1:40.

Control population

Two out of the four patients with pneumatosis also had an active, non-obstructive duodenal ulcer (Table I) at the time the diagnosis of pneumatosis was made. According to the literature gastric or duodenal ulcers (when obstructive) can cause pneumatosis [5]. Therefore we restudied all abdominal X-ray films of patients within our transplant population who had a gastric or duodenal ulcer in the period from 1971–1982. An active CMV infection was excluded in these patients when the ulcer was diagnosed. In 18 out of the 382 patients transplanted between 1971–1983 a gastric or duodenal ulcer had been proven. In 17 cases we had sufficient X-ray material to examine whether or not pneumatosis intestinalis had been present at the time the ulcer was found.

Results

The results are given in Table I. An example of the radiological features of pneumatosis is given in Figure 1 (patient No. 2). All four patients had active CMV infection at the time the diagnosis of pneumatosis was made.

In the case of patients Nos. 3 and 4 the diagnosis of pneumatosis was made retrospectively, one of which (patient No. 3) had no abdominal symptoms whatsoever. In case No. 3 the diagnosis was made retrospectively on the intravenous urogram performed at the time the patient complained of arthralgia. Patients Nos. 1, 2 and 3 underwent a complete recovery without surgical intervention. Patients 1 and 2 received oxygen therapy via Ventimask® which resulted in rapid disappearance of the radiological signs of pneumatosis intestinalis.

Patient No. 4 died in profound shock after severe untreatable gastrointestinal bleeding. At post-mortem examination disseminated CMV infection was found with multiple inclusion bodies in lungs and liver. Inclusion bodies were found adjacent to the vessels in the ulcers. CMV virus was cultured from these sites.

Control population

In none of the 17 patients with a proven ulcer could we find any evidence of pneumatosis at the time the ulcer was diagnosed.
Discussion

The incidence of active CMV infection was stated to be as high as 43–92 per cent in renal transplant patients [6]. Most of the cases are subclinical but when the CMV infection is clinical, the symptoms may show great variety. Well-known is the so-called ‘self-limited syndrome’, comprising about 40–50 per cent of the patients infected [6]. The self-limited syndrome usually occurs between the 30th and 90th post-operative day and consists of prolonged fever, arthralgia, leucopenia, abnormalities in liver enzymes, respiratory symptoms or/and infiltrates on chest roentgenogram, and impairment of renal function [6]. Other manifestations of CMV infection post-transplant are protean, comprising lymphadenopathy, rash, hepatosplenomegaly, conjunctivitis [6], vasculitis [7], CMV glomerulopathy and lethal, so-called ‘wasting’ CMV infection [6].
CMV has been noted to reside in alimentary tract ulcers [6], sometimes associated with vasculitis at the site of the ulcer [8].

Pneumatosis intestinalis is an uncommon disease whose pathogenesis is still under discussion [5]. The condition is often associated with intestinal obstruction, especially with pyloric obstruction due to a peptic ulcer. Associations also have been made with chronic pulmonary disease, collagen diseases associated with vasculitis (systemic lupus erythematosus, periarteritis nodosa), or motility disorders of the bowel leading to functional obstruction (scleroderma). Less frequently pneumatosis has been found in association with gastrointestinal infections with gas-forming bacilli, lymphoma and leukaemia.

Reports of pneumatosis intestinalis in renal transplant patients [1,9] are rare and are believed to be associated with the immunosuppressive drugs used [1,9]. Very recently the condition was described in three patients following allogeneic bone marrow transplantation [10]. Although the condition, according to the authors, was related to the immunosuppressive drugs used, it is interesting that two of the three patients also suffered from severe CMV infection (CMV oesophagitis, CMV-pneumonia) [10].

In this article we describe four patients with pneumatosis intestinalis after renal transplantation, all with concomitant severe CMV infection.

One can only speculate on the pathogenesis of the pneumatosis in these four patients. The negative findings in the control population could suggest that the ulcers per se were not the cause of the condition. None of the patients had chronic pulmonary disease, gastrointestinal infections with gas-forming bacilli, evidence of ischaemic bowel disease, or a systemic disease like lupus. The immunosuppression per se also seems unlikely as the sole pathogenic explanation, because of the low incidence of the condition in the whole transplant population. The striking coincidence with severe CMV infection in all four patients suggests that infection with CMV might be related to the condition.

Possible explanations could be the primary cytopathogenic effect of CMV on the intestinal mucosa or vasculitis due to the CMV infection. As mentioned above, CMV is often found in the gastrointestinal mucosa with or without ulcers [6,8], and with or without vasculitis [6,8].

In conclusion, we believe that pneumatosis intestinalis in a renal transplant patients might be associated with an active CMV infection. These data stress the importance of a keen awareness of the possibility of a CMV infection in renal transplant patients with free air under the diaphragm and/or abdominal symptoms. In these patients unnecessary surgery should thus be avoided.

References
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