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BRIEF REPORT

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Campylobacter jejuni bacteremia and Guillain-Barré syndrome in a renal transplant recipient

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Abstract In patients who have not undergone transplantation, Guillain-Barré syndrome (GBS) is typically preceded by an acute infection often sustained by *Campylobacter jejuni*. Thus far, in renal transplant recipients, only eight cases of GBS have been reported. In seven patients GBS was attributed to cytomegalovirus infection and in the eighth patient to cyclosporin A neurotoxicity. We report here the case of a GBS in a renal transplant recipient following *C. jejuni* bacteremia. The infection quickly disappeared after erythromycin and methronidazole therapy. GBS progressively evolved into a paraparesis within 1 week. After reaching a plateau phase, the clinical status improved and the patient was able to walk unassisted after 3 weeks. At his last check-up, 54 months later, the patient was doing well with a functioning graft and only minimal weakness of the lower limbs.

Key words Guillain-Barré syndrome, *Campylobacter jejuni*, renal transplantation · *Campylobacter jejuni*, Guillain-Barré syndrome, renal transplantation · Renal transplantation, *Campylobacter jejuni*, Guillain-Barré syndrome

Introduction

Guillain-Barré syndrome (GBS) is now considered to be the most common cause of acute, generalized paralysis. The most frequent clinical picture of GBS is that of an acute, monophasic disease due to an inflammatory, demyelinating polyradiculoneuropathy, affecting mostly the motor nerves [12]. Acute GBS typically starts with numbness and paresthesias of the extremities, followed by weakness of the limbs with reduced or absent tendon reflex. Weakness may begin in the lower limbs and then ascend to involve the trunk, the upper limbs, and the cranial nerves. About one-quarter of patients may need mechanical ventilation because of the involvement of the respiratory muscles. The weakness tends to worsen progressively, and in 1–3 weeks the patients become bedridden and, in severe cases, quadriplegic [25, 26]. GBS is considered to be a "postinfectious disease" since it occurs 1–3 weeks after an acute respiratory or gastrointestinal infection [12, 16, 24, 25]. Several etiological pathogens have been reported, including cytomegalovirus (CMV), Epstein-Barr virus, hepatitis-associated virus, respiratory viruses, enteroviruses, and mycoplasma [13, 25]. However, *Campylobacter jejuni* is now recognized as the agent most frequently involved in the infection that precedes GBS [7, 12, 13, 16, 24–26, 29].

GBS can also occur after renal transplantation, although it is rare. To the best of our knowledge, only eight cases of GBS have been reported in renal transplant recipients. GBS was associated with CMV infection in seven of these patients [4–6, 14, 23] and attributed to cyclosporin A (CyA) neurotoxicity in the eighth [20]. CMV infection was also considered the triggering event in two cases of GBS occurring in heart transplant recipients [3] and in one patient who underwent bone marrow transplantation (BMT) [22]. Finally, GBS has been reported to occur after high-dose chemotherapy in a patient who underwent BMT without any obvious

associated infection or immunosuppression [17, 18]. Thus far, to our knowledge, only one case of *C. jejuni* bacteriemia with subsequent development of GBS has been reported in a BMT recipient [9]. The association between *C. jejuni* bacteriemia and GBS has never before been described in renal transplant recipients.

In this report we describe a case of GBS that developed in a renal transplant recipient a few days after a *C. jejuni* bacteremia.

Case report

A 49-year-old man was found to be affected by diabetes mellitus in 1982. A few years later, a nephrotic proteinuria with progressive renal dysfunction developed (renal biopsy was not performed). The patient was referred to us with severe renal failure, and a few months later, in April 1991, he had to undergo peritoneal dialysis. In December 1992, at the age of 59 years, the patient received a cadaveric renal transplant that was 3/6 HLA-matched. Graft function recovered rapidly. Immunosuppression consisted of CyA alone at an initial dosage of 12 mg/kg per day. The patient suffered from two acute rejections (on the 12th and 26th postoperative days) that reversed after two courses of intravenous methylprednisolone (8 pulses, 0.5 g each). After the second rejection, oral methylprednisolone was added at a dose of 12 mg/day; this was tapered to 8 mg/day by the end of the 3rd month. The patient was readmitted to our unit on the 45th post-operative day because of a fever of unknown origin. The physical examination and chest X-ray were normal. The laboratory findings were not conclusive. The patient was treated with intravenous pefloxacin and recovered completely.

The patient remained well until the 196th post-transplant day, when he was readmitted to our unit because of fever (39 °C) and aching in the large muscles of the lower limbs, a 4-day history of low-grade fever, and a 48-h long, self-limited, nonbloody diarrhea. On admission, his blood pressure was 155/80 mmHg, his pulse rate was 96/min, and his respiratory rate was normal. The skin of the limbs showed mild purpura. The initial neurological examination revealed only tenderness of the thigh. A chest X-ray was normal. Laboratory findings revealed blood urea 110 mg/dl, serum creatinine 2.2 mg/dl, white blood cells 25,600/mm^3 with 95% neutrophils, 2.5% lymphocytes, 2% monocytes, hemoglobin 10.6 g/dl, platelets 231,000/mm^3, and normal levels of AST and ALT. Positive titers of IgG CMV and positive IgM CMV antibodies were detected. A CMV pp-65 antigenemia was negative. *C. jejuni* was isolated from five out of five blood cultures. The patient received intravenous erythromycin (2 g/day) for 5 days plus intravenous methronidazole (500 mg three times a day) for 9 days, followed by oral methronidazole (at the same dosage) for another 5 days, while the dose of CyA was reduced from 100 mg b.i.d. to 50 mg/day. With such a reduction, the trough blood levels of CyA remained between 150 and 250 ng/ml (monoclonal method). After the withdrawal of erythromycin, CyA was increased to 50 mg b.i.d.. In the following 6 days, fever abated. However, by the 3rd hospital day, the patient developed bilateral, symmetric leg weakness that made walking difficult and persistent aching in the large muscles of the flanks. The neurological examination revealed normal mental status, normal cranial nerve function, and symmetric lower limb weakness. The sensory examination showed only hyperesthesia of the lower limbs. Weakness progressively worsened to the point that the patient became bedridden within 1 week. At this point, the tendon reflexes of the patient's lower limbs were greatly diminished. There was no involvement of the respiratory muscles. A lumbar puncture was performed on the 4th hospital day. Cerebrospinal fluid (CSF) showed one leukocyte, a glucose level of 113 mg/dl, and a total protein concentration of 42 mg/dl (normal values 20–45 mg/dl). His serum contained high titers of IgM antibodies against GM1 ganglioside (1/1280) (normal titer < 1/640). A diagnosis of GBS was made. After a plateau phase, the patient's muscle power improved spontaneously. Finally, after 3 weeks, the patient was able to walk unassisted and was discharged. In the ensuing months, the neurological deficit recovered almost entirely and only minimal weakness of the lower limbs persisted. At his last check-up, the patient was doing well, with a serum creatinine of 1.4 mg/dl. Immunosuppression at the time consisted of CyA 125 mg/day, methylprednisolone 4 mg/dl, hypotensive drugs, and insulin.

Discussion

Campylobacter jejuni is now recognized as the agent most frequently involved in the infection that precedes GBS [7, 12, 13, 16, 24–26, 29]. To the best of our knowledge, this is the first documentation of a case of GBS that developed after a *C. jejuni* bacteremia in a renal transplant recipient.

In our patient, the rapidly progressive symmetric weakness in both legs that confined the patient to bed within 2 weeks, the diminished tendon reflexes, the mild sensory symptoms, the substantial spontaneous recovery, and the CSF without pleocytosis supported the clinical diagnosis of GBS, even in the absence of electrophysiological studies [2]. The protein concentration at the upper level of normality in the CSF, particularly in the early phase of the illness, as in our patient, did not exclude the diagnosis of GBS [26]. *C. jejuni* was isolated in all five blood cultures taken; moreover, our patient showed high titers of anti-GM1 IgM antibodies, as reported in other cases of GBS following a *C. jejuni* infection [8, 19, 31, 36]. Thus, it is very likely that our patient developed the GBS as a consequence of *C. jejuni* bacteremia. The patient had an adult-onset diabetes, but the diagnosis of diabetic polyneuritis was reasonably ruled out because of the acute onset, with predominant motor impairment, and the almost complete, spontaneous recovery, within a few weeks of onset, of the neuropathy [27]. Furthermore, high titers of anti-GM1 antibodies, though not specific for GBS and related syndromes, have not been associated with other forms of acute neuropathy [32]. The diagnosis of CMV infection was excluded by the negative pp-65 antigenemia, by the concomitant leukocytosis, and by the prompt recovery from fever after antimicrobial treatment. The possible involvement of CyA was hypothesized in a single case by Palmer et al. in the absence of other evident etiological factors [20]. The improvement in symptoms observed in our patient while continuing CyA makes any role for this drug unlikely.

Recovery over a period of weeks or months is a hallmark of GBS, but the majority of patients show some

persistent, minor residual deficit, such as footdrop, distal numbness or, less frequently, disabling weakness. Several reports have suggested that GBS associated with *C. jejuni* may constitute a more severe form of the disease [13, 24, 25]; however, other authors have reported that relatively mild cases may also occur [29]. Recently, the use of plasma exchange or intravenous immunoglobulin has been advocated to accelerate recovery from the disease in the most severe forms [15]. Since our patient rapidly reached a plateau phase, without involvement of the respiratory muscles and autonomic dysfunction, followed by a progressive improvement, we decided to treat him only with antibiotics active against *C. jejuni* and with supportive care. The patient was able to walk unassisted after 3 weeks, and in the ensuing 2 months he recovered his neurological deficit almost entirely. Only a minimal residual deficit has persisted until now.

It has been hypothesized that *C. jejuni* infection may trigger GBS by one or more of the following mechanisms: polyclonal lymphocyte activation, alteration of self-antigens to create partially crossreactive neoantigens, and crossreactivity to shared epitopes of nerves and microbes (molecular mimicry) [11]. The latter hypothesis is supported by the observation that some strains of *C. jejuni* may cause the production of antibodies against the organisms that crossreact with one or more myelin proteins [25]. Moreover, Yuki et al. have identified a crossreactive epitope contained in the lipopolysaccharide moiety of *C. jejuni* (serotype PEN 19) and in the ganglioside GM1 (a minor axolemmal glycolipid) isolated from a GBS patient with anti-GM1 ganglioside antibodies [34]. In GBS patients with *C. jejuni* infection, certain serotypes, such as PEN 19 or Lior 11, are greatly overrepresented compared to controls without neurological disease [10, 11]. Antibodies antiganglioside GM1 have been detected in patients with GBS [8, 19, 31, 36]. It is of interest that about 50 % of patients with anti-GM1 antibodies have evidence of preceding *C. jejuni* infection [12, 31]. However, in spite of these findings, the role of such mimicry in GBS remains hypothetical. In addition, the host's immunogenetic background may be important. A large study showed a weak association between GBS and HLA-DR2 [33], while Yuki et al. [35] reported that all six patients who developed GBS after *C. jejuni* enteritis had the HLA-B35 antigen. Therefore, these preliminary observations suggest that a patient may need to have particular HLA specificities, as well as to be infected with a certain strain of *C.jejuni,* before going on to develop GBS [25].

Humoral immunity is believed to be important in protection against *C.jejuni* infection. Sustained bacteremia has been reported in patients with HIV infection and hypogammaglobulinemia [1, 21, 30] and in an asymptomatic patient undergoing BMT [28]. Thus, the role of immunosuppressive therapy in the development of GBS remains unknown. Theoretically, immunosuppressive therapy may have a double-edged effect. It may potentially prevent the antibodies' response, thus protecting the patient from over-involvement; on the other hand, it can expose the patient to an increased risk of infections, including those sustained by *C. jejuni.*

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