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Changing images of cytomegalovirus infection

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CHAPTER 8

INFLAMMATORY DEMYELINATING POLYNEUROPATHY IN A KIDNEY TRANSPLANT PATIENT WITH CYTOMEGALOVIRUS INFECTION

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ABSTRACT

This is a case report about a renal transplant recipient with inflammatory demyelinating polyneuropathy during cytomegalovirus infection. It suggests that replication of cytomegalovirus is accompanied by flare-ups of the polyneuropathy. We speculate about the pathogenesis of the polyneuropathy in relation with cytomegalovirus infection.

8.1 INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare disease with a prevalence of approximately 1/100.000 in the general population [1]. The pathogenesis of the demyelination is thought to be immune mediated but the mechanism is uncertain [2]. Antecedent infections are reported in 35% of the patients with CIDP, especially cytomegalovirus (CMV) infections [3]. The CMV infection probably triggers an immune reaction against components of peripheral nerve myelin, for instance myelin associated glycoprotein/sulfated glucuronyl paragloboside [4].

Although CMV infections occur frequently after kidney transplantation demyelinating polyneuropathy is very rare in organ transplant recipients. In contrast CIDP is relatively frequent in patients with the acquired immunodeficiency syndrome (AIDS) and a relationship with CMV infection is suspected [5, 6, 7]. This is the first case report of a patient after renal transplantation with chronic inflammatory demyelinating polyneuropathy reflecting recurrence of viremia, suggesting that active replication of CMV may be accompanied by flare ups of the CIDP. We speculate about the pathogenesis of CIDP in this patient.

8.2 CASE REPORT

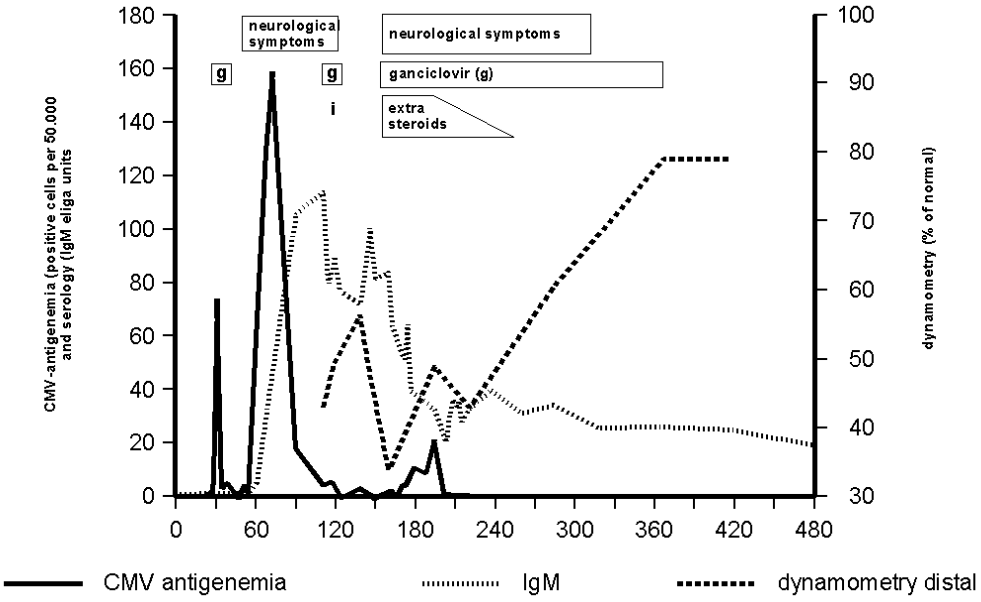
A 58-year-old male patient received a renal transplant in our hospital on 3 February 1996. The cause of his renal insufficiency was chronic glomerulonephritis. In September 1989 peritoneal dialysis (CAPD) had been started. Apart from appendectomy, hemorrhoidectomy and CAPD peritonitis his medical record was uneventful. The donor was a 47-year-old male who had died of cerebral trauma in a traffic accident. The donor was seronegative for HIV, HBV, and HCV but seropositive for CMV. Our patient was seronegative for CMV, HIV, HBV and HCV. The donor was mismatched for one HLA B and HLA DR. Crossmatches were negative.

The kidney was transplanted in the right iliac fossa using the external iliac vein and artery. Immunosuppressive therapy consisted of cyclosporine (Sandimmune, Novartis, Switzerland) and low-dose prednisolone. No CMV prophylaxis was given. Postoperatively there was immediately a good diuresis and the serum creatinine decreased to 154 μmol/l on the 7th postoperative day. From postoperative day 8 the serum creatinine started to rise as result of interstitial rejection graded Banff 1 [8]. Rejection was treated with 5 x 1g methylprednisolone (Solumedrol, Kalamazoo, MI) intravenously (i.v.) and because of unresponsiveness followed by 3 x antithymocyte

globulin 4 mg/kg (Rabbit ATG, Merieux, France) on days 20,23 and 26. Maximum serum creatinine was 565 μmol/l and decreased to 174. ATG was given only three times because of persistent thrombocytopenia (nadir 42 10^6/l) and leukopenia (nadir 0.5 10^9/l granulocytes) as well as a positive cytomegalovirus pp65-antigenemia assay [10, 11] indicating a primary CMV infection. The only symptom the patient had that time was a slightly elevated body temperature of 38.5 C. As soon as the diagnosis of primary CMV infection was made i.v. therapy with ganciclovir was instituted on day 27. Maximum antigenemia was 75 CMV pp65-positive cells per 50 000 polymorphonuclear cells ($75/5.10^4$) during ganciclovir that was continued until day 46. After stopping ganciclovir, antigenemia increased again with a maximum of $158/5.10^4$ on day 73. On day 59 the patient noticed cold numb fingertips and toes. Later these started aching. Pain and numbness slowly progressed towards the wrists and entire lower legs. On day 116 he noticed diminished strength in arms and legs. He could not lift his teacup and climb the stairs. This loss of strength also was progressive. There were no disturbances in defecation or micturition. On neurological examination a paresis of legs and arms (distal more than proximal) was found. Loss of strength was measured with a hand-held dynamometer and expressed as percentages of the predicted values. He could not walk on his toes or heels. Hypaesthesia, hypalgesia and loss of vibration sense were found distally from knees and wrists. Neurophysiological examination showed reduced motor nerve conduction velocities, with absent F-waves and H-reflexes. On needle examination no denervation was found.

A diagnosis of chronic demyelinating polyneuropathy was made. Antigenemia assay was positive indicating ongoing CMV infection. A rise of CMV IgM and later IgG antibody showed that the patient developed an immune response against CMV [9]. A polyclonal hypergammaglobulinemia was found. Cerebrospinal fluid (CSF) protein level was elevated (1.3 g/l; normal < 0.5 g/l) and CMV IgG antibodies were found in the CSF. During treatment with immunoglobulins (Central Laboratory for Blood transfusion, Amsterdam, the Netherlands) 0.4 g/kg i.v. during 5 days and ganciclovir (days 115-122) the patients neurological symptoms improved dramatically (figure 8.1). Antigenemia became negative. On day 154, however he developed a distal grade 3 and proximal grade 4 paresis of the legs and arms again. Hypaesthesia of hands and lower legs and loss of vibration sense became evident. Antigenemia was again positive in low numbers of positive cells and showed a tendency to rise, indicating an increasing viral load. We treated him with ganciclovir again and prednisolone 100 mg for 6 weeks and tapered it in two months to 10 mg orally. Ganciclovir was continued orally for one year. He slowly improved neurologically and antigenemia assay became negative.

Figure 8.1 Clinical course and serial values of CMV pp65-antigenemia (number of p65-positive polymorphonuclear cells per 50.000 pmn cells), CMV-IgM and dynamometry of distal muscles (percentages of predicted values) in this patient. Immunoglobulins abbreviated as i, ganciclovir as g.



8.3 DISCUSSION

This patient developed a progressive demyelinating polyneuropathy 4 weeks after beginning of CMV infection, during a second flare up of CMV antigenemia, and during the appearance of CMV-IgM antibodies. Initially there was a good response to immunoglobulins [12] and ganciclovir, but after stopping the ganciclovir the polyneuropathy became worse during a smouldering CMV infection. The patient improved with high-dose steroids and oral ganciclovir.

The pathogenesis of the neuropathy remains speculative. In AIDS patients CMV has been found in the nerves and there is a good response on therapy with ganciclovir [13, 14]. In our patient the relapse of the neuropathy after stopping ganciclovir, followed by the recurrence of the virus in the blood as well as the good response after restarting treatment with ganciclovir, is an argument for a causal relationship with CMV infection. However, clinically the neuropathy was quite different from the ordinary CMV-induced neuropathy, which is mainly sensory and axonal. On the other hand the course of CMV-IgM also parallels the neuropathic symptoms in this

patient. This might suggest, together with the considerable improvement after the instigation of high-dose immunoglobulin therapy, an antibody mediated autoimmune process [15, 16]. Yuki et al. [4] found a correlation between the presence of cytomegalovirus DNA and a myelin antibody (ant-Mag/antiSGPG) in the sera of patients with chronic polyneuropathy.

Another possible explanation is a T-cell-mediatedauto-immune response against myelin. Structural similarity between viral T-cell epitopes and self-peptides could lead to the induction of an autodestructive T-cell response [17]. In contradiction to this explanation might be that we treated our patient with aggressive polyclonal anti T-cell therapy (ATG) before the development of CIDP.

CIDP is a regularly observed phenomenon in AIDS patients during CMV infection. There are several possible explanations for the differences in incidence of CIDP in the AIDS population compared to transplant recipients. First, HIV may destroy nerves by direct infection of the nerves by the virus. Second, although AIDS patients are also immunosuppressed, the nature of this suppression differs considerably, which might reflect differences in sequelae leading to a possible autoimmune process elicited by the viral infection. Third, the duration of viremia might be important. In the transplant population the duration of viremia is usually short, being confined mostly to the period of maximum immunosuppression, i.e. shortly after initiation of anti-rejection therapy. In the majority of patients with eventually low-dose immunosuppression after completion of the antirejection treatment, the virus will remain in a latent state after antiviral treatment and the subsequent immune response. In contrast, in the AIDS population, prolonged CMV viremia is the rule, which might be a prerequisite for the development of autoimmune phenomena. Our patient is characterized by an unusually prolonged period of CMV viremia, which might have been a crucial factor for the development of CIDP in this particular case.

In conclusion, this report clearly demonstrates the course of chronic inflammatory demyelinating polyneuropathy during recurrent CMV viremia and CMV IgM immune response. A causal relationship between CMV infection and polyneuropathy is suggested. The question whether the virus itself or the immune response is responsible for the polyneuropathy remains to be resolved.

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