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Cachexia and tumour necrosis factor- α in cytomegalovirus infection

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Abstract

Although cachexia is a common feature of cytomegalovirus infection, little is known about its cause. To explore any contributory role that tumour necrosis factor- α (TNF) might have the serum concentrations of TNF in eight patients who developed CMV disease after liver transplantation were investigated. All patients exhibited pronounced and long lasting increases in TNF serum concentrations. Increased endogenous TNF concentrations were associated with weight loss and anorexia. In contrast, liver transplant recipients without CMV disease showed no weight loss.

Cachexia has long been recognised as a prominent feature of patients with CMV infection. The cause of the profound weight loss and anorexia in these patients remains unclear. Tumour necrosis factor- α (TNF) is a macrophage-derived cytokine implicated in host defense against tumour cell growth and infection.¹ Experimental and clinical studies have suggested a role for it in inflammation, cachexia, and tissue injury.^{2,3} Recently, we have shown that enhanced endogenous production of TNF, interferon- γ , β -2-microglobulin and neopterin is a regular feature of inflammatory complications after liver transplantation.⁴ The aim of this study was to investigate TNF serum concentrations in patients with CMV infection after liver transplantation and to assess their potential role in the pathogenesis of cachexia associated with CMV infection.

Methods

Eighteen liver transplant recipients were studied. These transplantations had been performed in patients with chronic liver disease

(chronic active cirrhosis in 10, primary biliary cirrhosis in five, hepatocellular carcinoma in three). Patients received prophylactic immunosuppressive treatment consisting of methylprednisone, azathioprine, and cyclosporine A. Acute graft rejections were treated with gram bolus doses of methylprednisone.

During the early postoperative period, 10 episodes of reversible rejection were observed. Eight patients developed CMV infection. Ten patients showed no complications in the later postoperative course. These patients were used as a control group.

CMV disease was defined on the basis of serological demonstration of a CMV specific antibody response combined with clinical symptoms. Symptoms suggestive of CMV disease were cytopenia, interstitial pneumonia, liver dysfunction and otherwise unexplained fever. To corroborate the diagnosis throat swabs, urinary samples, and blood buffy coats were used for CMV cultures. Day 0 of CMV disease was defined as the first day with positive virus culture in conjunction with clinical symptoms.

Serum samples were obtained twice weekly and stored at -20°C . Serum concentrations of TNF were assayed with a commercially

Mean (SEM) TNF serum concentrations and weight loss in eight patients with CMV disease

Day*	TNF (pg/ml)	Body weight (kg)
-10	15.1 (3.3)	63.4 (4.9)
-5	27.6 (9.4)	61.9 (5.3)
0	42.3 (7.5)	60.5 (5.5)
5	48.9 (8.9)	59.5 (5.7)
10	42.3 (6.3)	60.6 (6.9)
15	67.0 (13.2)	57.9 (5.6)
20	41.7 (17.1)	56.0 (5.7)
30	52.7 (11.5)	52.3 (6.9)

*Day 0 defined as first day with positive virus culture in conjunction with clinical symptoms.

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available competitive inhibition radio-immunoassay (IRE-Medgenix, Fleurus, Belgium; lower detection limit of > 5 pg/ml). Patients were considered cachectic when their weight was less than 85% of the predicted ideal body weight compared with controls matched for age, sex, and height enrolled in the Health and Nutrition Examination Survey.⁵ Data were expressed as mean (SEM).

Correlations were analysed using the Pearson correlation coefficient.

Results

CMV infection in patients was predominantly seen in the seventh postoperative week (range fourth to ninth postoperative week). Eight patients developed CMV infection. They had significantly higher mean serum concentrations of TNF (42.16 (4.3) pg/ml) than the 10 control patients (8.3 (2.1) pg/ml; $p < 0.001$). TNF serum concentrations were already increased as early as day 0 of CMV infection and maximum concentrations were reached between day 5 and 15 (table). All patients showed increased TNF serum concentrations which persisted for about four weeks. The rise in TNF concentrations paralleled clinical symptoms. Treatment with ganciclovir and clinical improvement were accompanied by a rapid fall in TNF. Two patients died of CMV disease. They both presented with interstitial pneumonitis and severe wasting. Patients with acute cellular rejection ($n = 10$) also showed increased TNF serum concentrations (47.5 (5.7) pg/ml). After successful rejection treatment, however, TNF serum concentrations rapidly returned to normal in this group. The control group without any complication in the late postoperative period ($n = 10$) showed low and stable TNF serum concentrations.

Four of the eight patients with CMV disease were cachectic (body weight less than 85% of ideal) at day -10 (61.4 (4.9) kg), while at day +30 seven of the eight were cachectic (52.3 (6.9) kg) (table). In the control group two out of the 10 patients were cachectic before transplantation; in the subsequent postoperative course body weight did not change significantly in this group. Significant weight loss was not observed in the early postoperative period, where patients only showed intermittently increased TNF serum concentrations.

Discussion

The findings of this study indicate that there are long term increases in TNF serum concentrations in patients with CMV infection after liver grafting. All eight patients with CMV infection developed severe weight loss in contrast to the patients who showed stable body weight and an uncomplicated recovery course following transplantation. Transient increases in endogenous TNF concentrations lasting only a few days as seen in cases with acute cellular rejection were not followed by clinically important weight loss.

In various animal models long term administration of TNF induced anorexia, weight loss, loss of body protein and death.^{6,7} As all our patients with CMV disease exhibited increased concentrations in TNF over a period of one month, there may be an association between cachexia associated with CMV disease and TNF. TNF antibodies have been shown to protect against the lethal effects of septic shock and cachexia.¹⁸ Whether such an approach can mitigate the effects of cachexia in severe CMV disease needs to be evaluated further.

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