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Daily Serum Interleukin-6 Monitoring in Multiple Organ Transplantation With or Without Liver Allografts

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WE PREVIOUSLY reported that daily monitored serum or plasma interleukin-6 (IL-6) levels maybe a good premonitor of liver allograft rejection and also a useful predictor of long-term graft prognosis.¹

Histopathologically, liver allograft rejection is characterized by a cellular infiltration consisting mainly of monocytes/macrophages and activated T lymphocytes. IL-6 is an inflammatory cytokine mainly secreted by monocytes/macrophages and endothelial cells. Kupffer cells and vascular endothelial cells in the liver may also secrete IL-6. Therefore, both infiltrating host immune cells and allograft cells (activated Kupffer and endothelial cells) may play a role in producing IL-6. The liver is the largest organ in the human body and potentially produces IL-6. The liver is also the major target organ of IL-6.

To clarify this phenomenon (ie, that the major source of IL-6 is the liver allograft), we evaluated sequential serum IL-6 levels in various organ transplants with and without liver allografts.

SUBJECTS AND METHODS

FK 506 or cyclosporine (CyA), to which various doses of methylprednisolone were added, were used for baseline suppression. OKT3 was given when indicated. Daily monitoring of serum IL-6 was performed in cases of 18 kidney, 27 liver, 5 lung (single lung: 2, double lung: 3), 1 small bowel, 4 liver + kidney, 5 liver + islet (abdominal organ cluster transplantation), and 3 liver + small

Table 1. Number of Various Organ Transplants Undergoing Serum IL-6 Monitoring

Transplants	Cases
Kidney	18
Liver	27
Lung	5*
Small bowel	1
Liver + kidney	4
Liver + islets (cluster)	5
Liver + small bowel	3
Total	63

*Single: 2; double: 3.

bowel transplantation using ELISA (Table 1). ELISA was performed using a two-step sandwich enzyme immunoassay method with Quantikine (Research and Diagnostic Systems Inc. Minneapolis, Minn.) as described elsewhere.¹ Daily monitored IL-6 levels were evaluated and compared to clinical courses and histopathological diagnosis of rejection in all cases.

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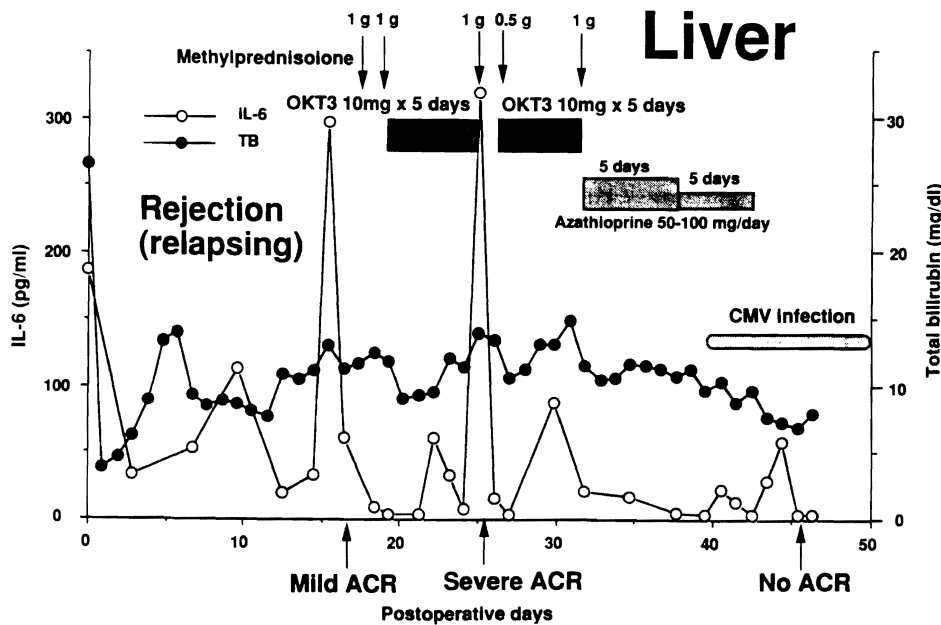


Fig 1. A 52-year-old woman with alcoholic cirrhosis underwent liver transplantation. She had many relapsing rejection episodes.

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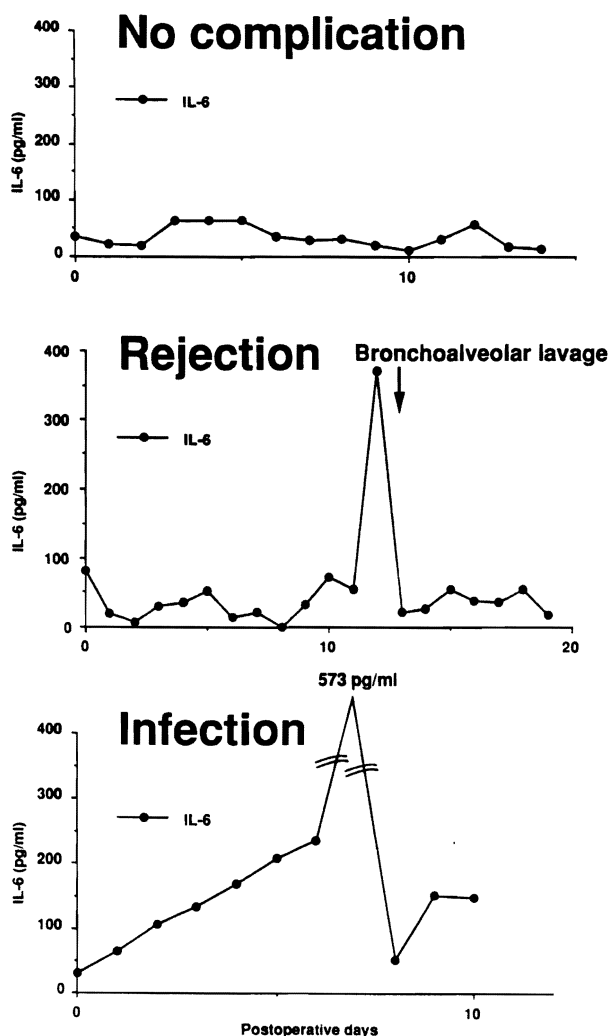


Fig 2. Serum IL-6 monitoring in lung transplant recipients. Upper: Double-lung transplant recipient with no complications. Middle: Single-lung transplant recipient with one rejection episode. Rejection was confirmed by bronchoalveolar lavage (BAL). An IL-6 spike was observed 1 day before BAL. Lower: Double-lung transplant recipient with bacterial infection in both lung allografts. IL-6 levels were consistently high.

RESULTS

The normal mean value of IL-6 from 30 healthy volunteers was 18 ± 34 pg/mL, of whom 21 (70%) had nondetectable (<10 pg/mL) levels. We defined the normal IL-6 cutoff levels as 86 pg/mL, which was the mean ± 2 SD value of the 30 healthy volunteers.

The mean number of IL-6 measurements averaged 16.5 per patient. All patients with infection subsequently developed continuously high IL-6 levels. Rejection episodes occurred in five cases (proven histopathologically by eight biopsies) in kidney transplantation. However, no spike-shaped IL-6 elevations (>86 pg/mL) were found in these cases.

In liver and liver + islet transplantation, serum or plasma levels of IL-6 were decreased after liver (or liver + islet) transplantation, regardless of pretransplant values. Patients with infection subsequently developed continuously high IL-6 levels. In patients without infection, significantly higher levels of IL-6 were usually found prior to the histopathological diagnosis of rejection. IL-6 elevation was spike-shaped, correlated poorly with the histological grade of rejection, and was highly responsive to augmented immunosuppression. One representative case with late-phase relapsing rejection episodes is shown in Fig 1. On the same day or one day before the biopsy showing acute cellular rejection (ACR), an IL-6 spike was observed.

Similar to the case with liver transplants, histopathological rejection episodes involving lung allografts showed spike-shaped IL-6 elevations 0 to 2 days before histopathological diagnosis of rejection. Representative cases of no complication, rejection, and infection are shown in Fig 2.

In the case of small bowel transplantation, no IL-6 elevation was observed during mild ACR on postoperative day (POD) 6 and the prominent ACR on POD 14. Since prominent ACR was proved on POD 14, antirejection therapy was initiated soon and treated successfully (Fig 3).

In contrast, in transplantations combined with liver allografts (liver + small bowel and liver + kidney), if the rejection episodes were found in the liver allograft, IL-6 spikes were also found 0 to 4 days before histopathological rejection. Interestingly, even with rejection episodes in other allografts (small bowel or kidney), IL-6 spikes were also found in the same fashion.

A 4-year-old boy with gastroschisis (Fig 4) underwent liver + small bowel transplantation. Neither the liver nor small bowel biopsy showed any histological rejection in this case. Although liver biopsy on POD 15 showed no signs of rejection, serum glutamate oxaloacetate transaminase (GOT) levels rose again on POD 16, indicating liver dysfunction possibly due to rejection. An IL-6 elevation spike was observed on POD 13.

A 26-year-old woman with superior mesenteric artery thrombosis (Fig 5) underwent liver + small bowel transplantation. Biopsies showed no signs of liver rejection, but clinical rejection was diagnosed by the rise in serum total bilirubin (TB) levels. Methylprednisolone bolus (1 g) was administered and liver rejection appeared successfully treated on POD 25. Biopsies undertaken on POD 25 and 35, however, showed rejection of the small bowel allograft. During this period (POD 25 to POD 35), IL-6 spikes were also observed.

A 44-year-old man with primary sclerosing cholangitis and polycystic kidney underwent combined liver and kidney transplantation, and the posttransplant course was uneventful (Fig 6). Serum IL-6 levels were always in the normal range.

A 40-year-old man with cryptogenic cirrhosis and chronic renal failure underwent combined liver and kidney transplantation (Fig 7). Biopsies of both kidney and liver allografts showed no signs of rejection; however, he suffered

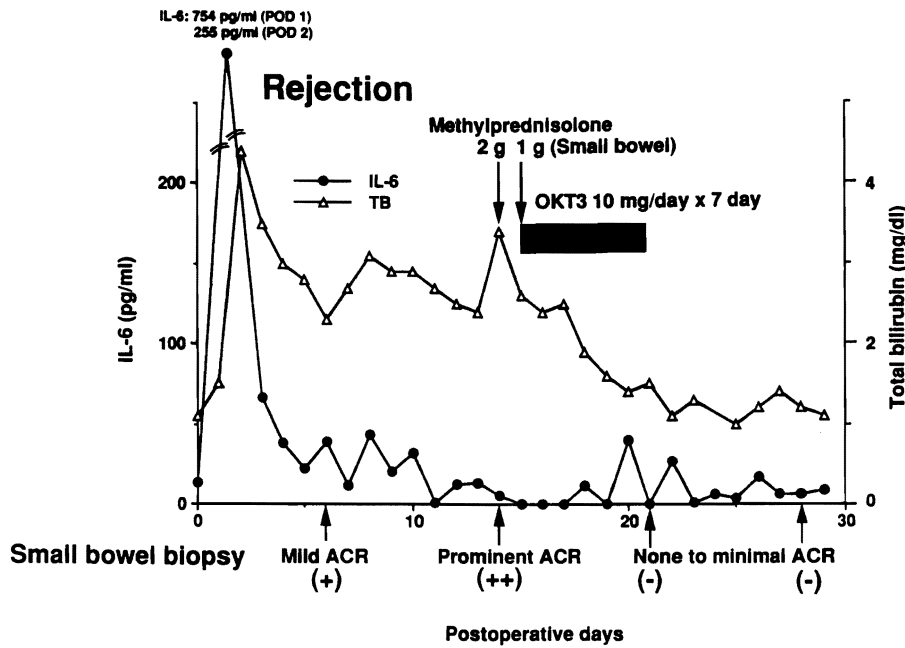


Fig 3. A 31-year-old man with gunshot injury to the superior mesenteric artery underwent small bowel transplantation. The serum IL-6 level was high POD 1 to 2 but decreased afterward, and stayed within the normal range regardless of biopsy-proven acute cellular rejection (ACR) episodes.

from bacterial and fungal infection after POD 10. IL-6 levels were very high after POD 10 except for a few days.

In the case of a 29-year-old man with cryptogenic cirrhosis and chronic renal failure (Fig 8), the direct crossmatch test showed strong positive. Kidney biopsy on POD 18

showed mild to moderate ACR and vascular rejection, and liver biopsy showed no ACR. IL-6 spikes were observed on the day of biopsy (POD 18) and POD 16. This patient suffered from overwhelming relapsing kidney rejection that necessitated nephrectomy after POD 50. The liver allograft

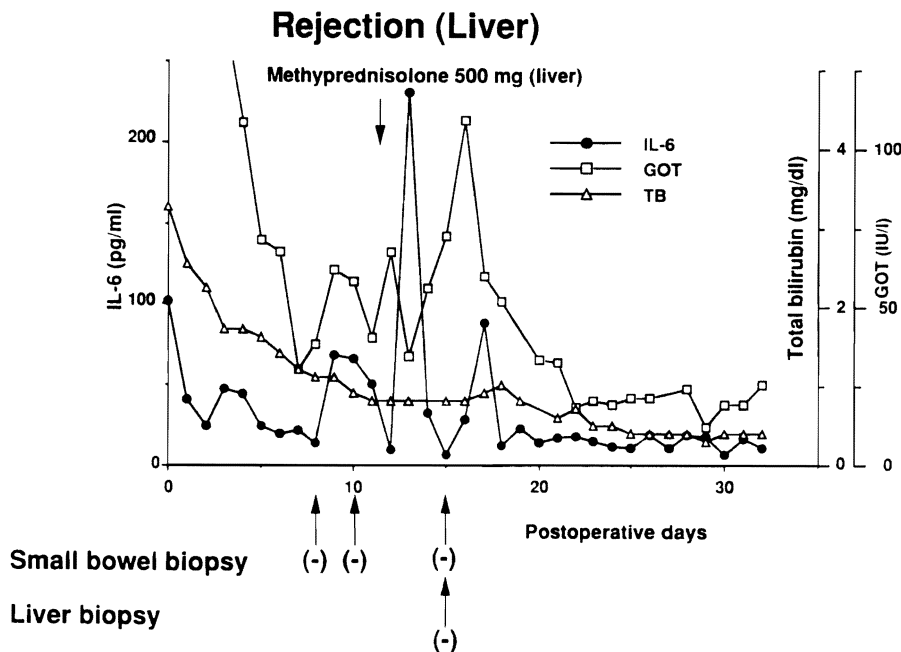


Fig 4. A 4-year-old boy with gastroschisis underwent combined liver and small bowel transplant. One gram of methylprednisolone was administered for clinically suspected liver allograft rejection.

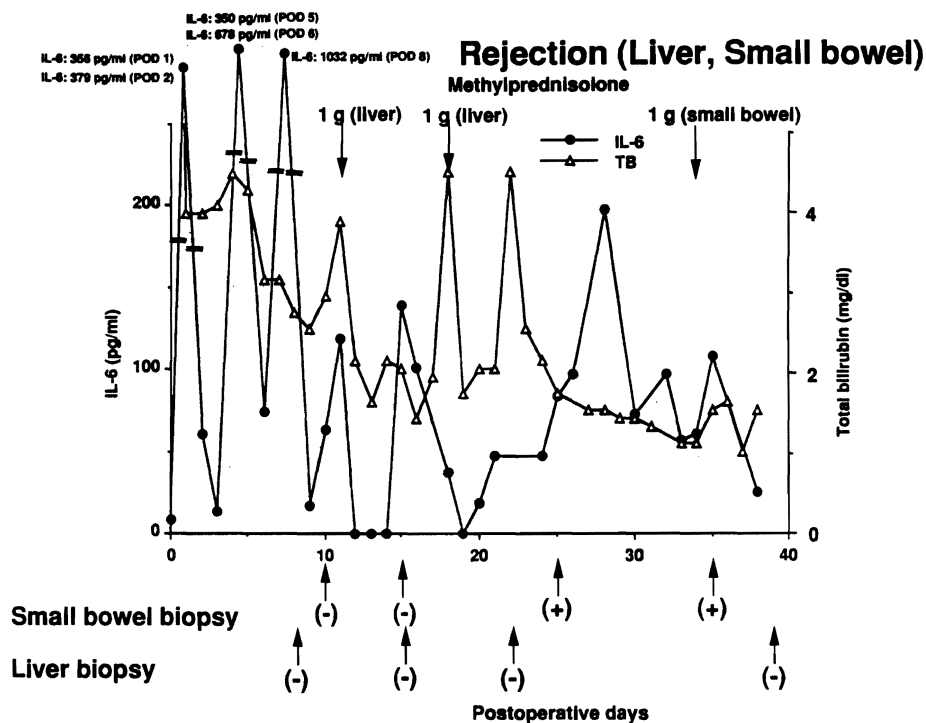


Fig 5. A 26-year-old woman with superior mesenteric artery thrombosis underwent combined liver and small bowel transplant. The first and second administration of methylprednisolone (1 g) were for liver allograft rejection. The third was for small bowel allograft rejection.

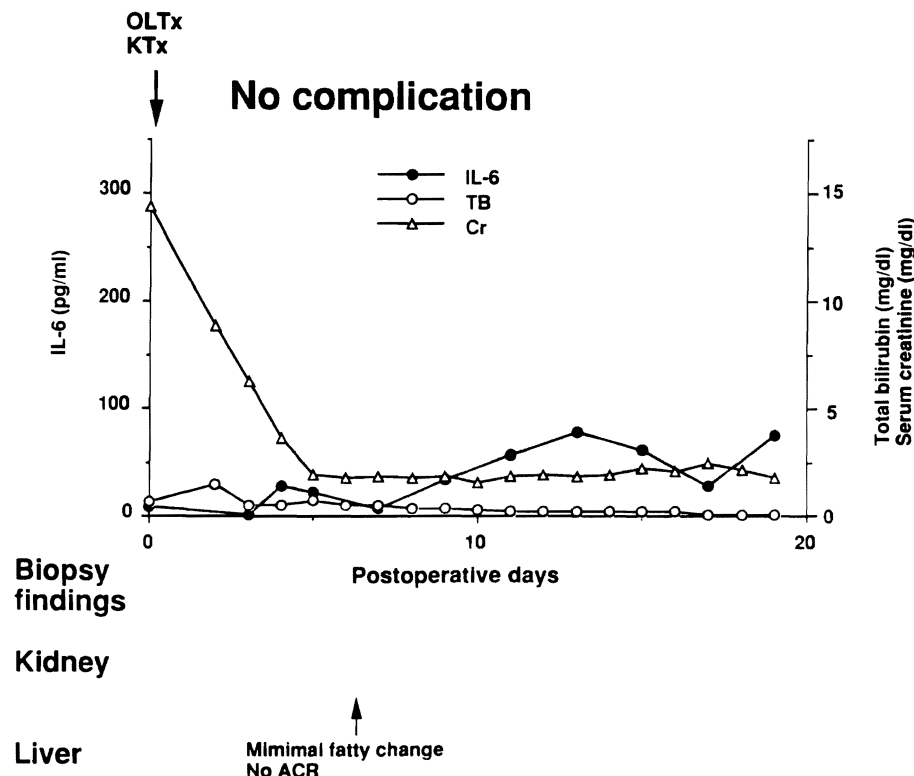


Fig 6. A 44-year-old man with primary sclerosing cholangitis and polycystic kidney underwent combined liver and kidney transplantation. The posttransplant course was uneventful.

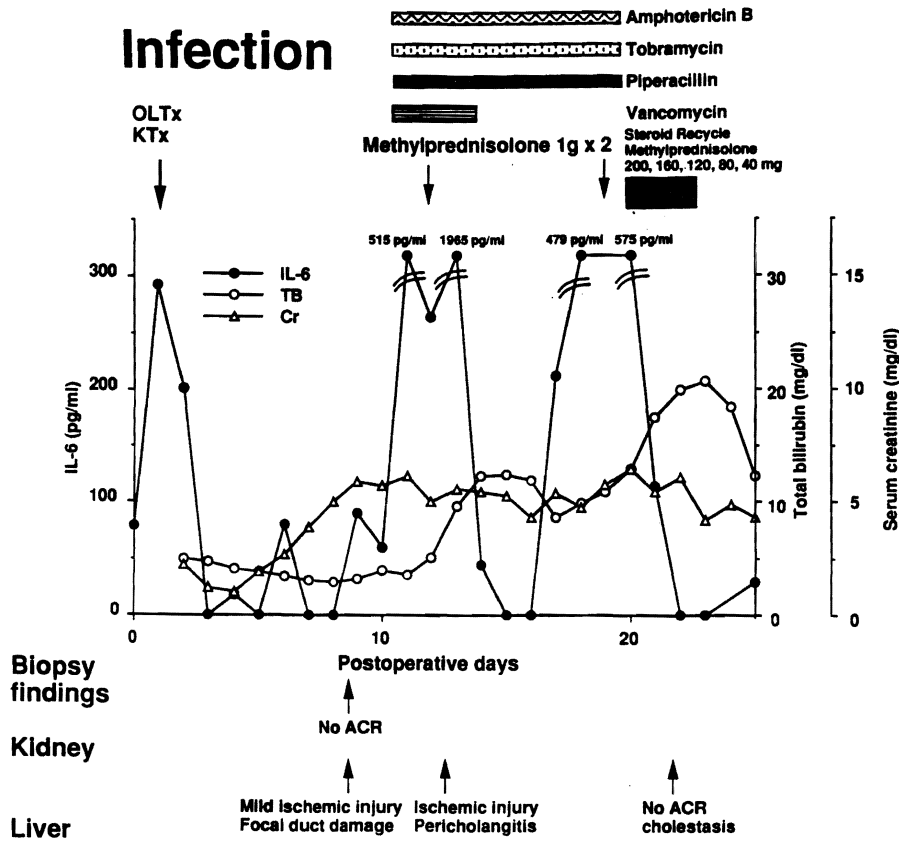


Fig 7. A 40-year-old man with cryptogenic cirrhosis and chronic renal failure underwent combined liver and kidney transplantation. He experienced bacterial and fungal infection after POD 10.

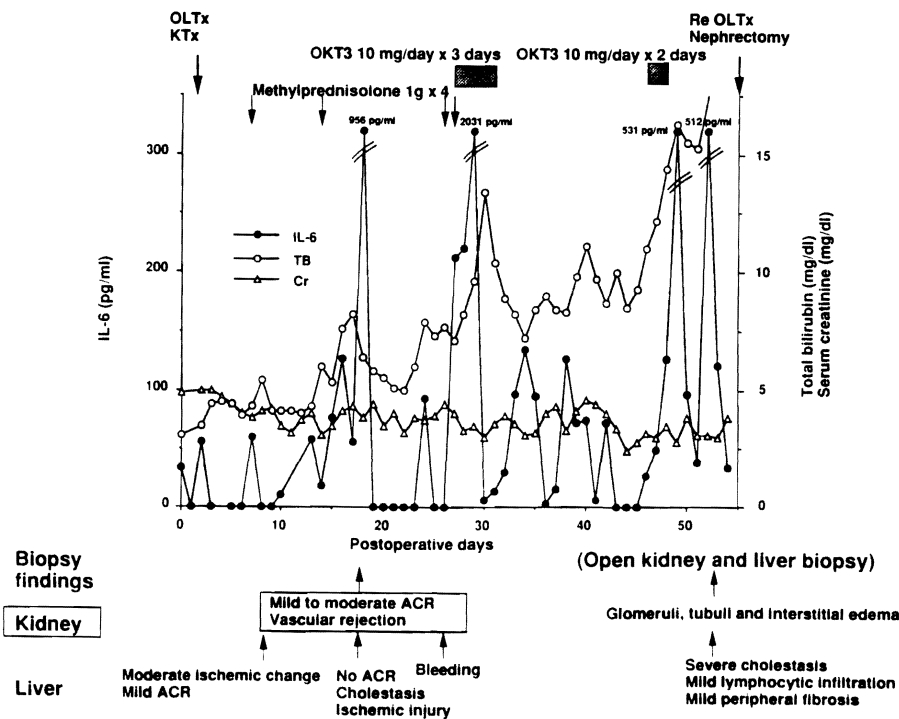


Fig 8. A 29-year-old man with cryptogenic cirrhosis and chronic renal failure underwent combined kidney and liver transplantation. He experienced relapsing rejection of the kidney allograft and subsequently underwent nephrectomy and liver retransplantation.

was also damaged due to ischemic injury and possible rejection proven by open liver biopsy on POD 52. Until this procedure, many IL-6 spikes were observed.

DISCUSSION

In this study, we have shown that daily monitoring of serum IL-6 levels are useful in the diagnosis of graft rejection in recipients with liver allografts. Liver and possibly lung allografts may produce much more IL-6 than kidney allografts during rejection episodes.

Although Yoshimura et al² reported the efficacy of IL-6 in diagnosing renal allograft rejection, we could not detect high levels of serum IL-6 in kidney transplants, even in biopsy-proven rejection episodes found in five cases (eight biopsies). This is mainly attributable to the sensitivity of assay because Yoshimura et al used a bioassay method more sensitive than ours.

Putting the ELISA assay sensitivity aside, in kidney or small bowel transplantation with liver allografts, we found significantly higher IL-6 concentrations in serum even when kidney or small bowel allografts were rejected.

These results suggest that allografts of the liver and lung, which are relatively large organs compared to the kidney, may be major sources of IL-6 production during allograft rejection because the liver and lung contain many monocytes/macrophages and large vascular endothelial beds, and also may have many infiltrating activated T cells at the time of rejection.

Hoffmann et al³ also suggested that the localization of tumor necrosis alpha (TNF- α)-producing cells correlated with the distribution of monocytes and macrophages in liver allografts and that concomitant plasma levels were elevated compared to those of controls without complications. Since it is well known that TNF- α induces IL-6 production, our findings also imply the intragraft production of inflammatory cytokines during rejection episodes.

Recently, Matsumoto et al⁴ reported that IL-6 participates in the regulation of human biliary epithelial cell growth in vitro. The ability of IL-6 to directly promote bile duct epithelium DNA synthesis provides a link between liver inflammation such as allograft rejection and the repair response. Thus, the control of inflammatory cytokines is important to obtain longer graft survival without biliary epithelial growth such as vanishing bile duct syndrome.

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