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Combined liver and islet transplantation: about one case

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Sir: The first attempt to perform combined liver and islet transplantation was made by Tzakis et al. [15] in patients submitted to modified cluster transplantation [14–16]. Subsequently, the same authors extended the indication of this treatment to patients affected with end-stage liver disease and type I diabetes [5,9], but the results were not very encouraging since none of the patients obtained an insulin-free condition. The same thing happened after combined kidney and islet transplantations performed by the same researchers.

In the early 1993, a 43-year-old female patient affected with end-stage HCV-related cirrhosis underwent observation in our hospital and was subsequently placed on our waiting list for liver transplantation. At the same time, it became evident that she was suffering from a serious form of type II diabetes with an impaired endogenous pancreatic function since her C-peptide levels after oral glucose stimulus were less than 1 μg/l. The patient needed a daily intake of more than 120 units of insulin; yet, a normalization of glycosylated hemoglobin levels was not obtained.

In July 1993, liver transplantation was performed in our unit in Padua using an ABO isogroup graft with negative crossmatch following the traditional technique. Organ reperfusion was excellent. At the same time, the donor's pancreas was sent to Verona where 250,000 islets were isolated and purified according to the technique described by Ricordi et al. [2, 7, 10]. The islets were then transported to Padua and injected into the recipient through a jejunal vein. They subsequently became diffused throughout the entire vascular bed of the liver graft.

In the postoperative period (Fig. 1), immunosuppression was based on cyclosporin and steroids at the usual dosages. No surgical complications occurred, but a rejection episode on the 5th postoperative day required a steroide pulse and recycle. On the 10th postoperative day, sepsis due to *Pseudomonas aeruginosas* led the patient to coma with anuria and pulmonary insufficency. This critical clinical condition was overcome by antibiotic therapy and a reduction in immunosuppression; sepsis disappeared and multiorgan failure was avoided.

The patient was discharged on the 120th postoperative day. Her last liver biopsy demonstrated a normal histological picture and, until now, the patient's general condition is satisfactory, with good liver function and only moderate renal dysfunction.

Throughout the same time period, secretory activity of the islet was followed with daily monitoring of blood glucose, C-peptide, and glucagon levels (Fig. 2). During the first 10 postoperative days, we saw a good engraftment of the islets since C-peptide levels were higher than 10 μg/l, but the need for exogenous insulin was very high (> 150 units daily). Despite the early complications, which required a steroid pulse and recycle and a long period of parenteral nutrition, in the days that followed, blood glucose and basal C-peptide levels returned to within the normal ranges, and subsequently the

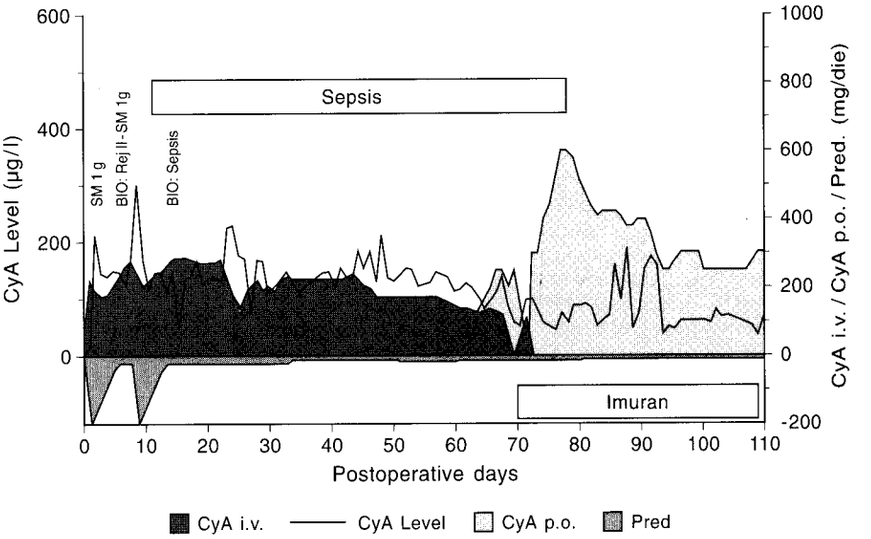

Fig. 1 Immunosuppression (*SM* Solumedrol, *BIO* biopsy, *Rej II* second degree rejection, *CyA* cyclosporin A, *Pred* prednisolone)

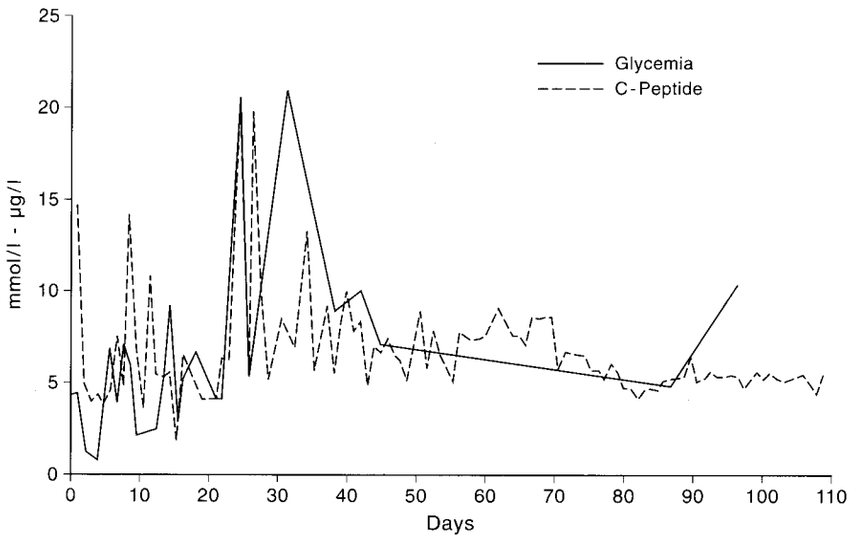

Fig. 2 Daily glycemia and C-peptide levels

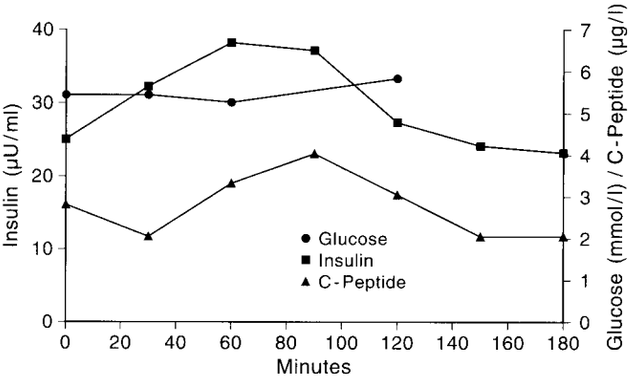

Fig. 3 Oral glucose tolerance test (OGTT). Glucose, insulin, and C-peptide blood levels

need for exogenous insulin decreased dramatically. When oral intake was resumed, we were able to observe the euglycemic conditions of the patient. At discharge, blood glycemia was normal, as were C-peptide and glycosylated hemoglobin levels, without any insulin intake. An oral glucose tolerance test (OGTT) revealed a delay in the peak C-peptide and in the insulin response, as well as a delay in the decrease of blood glucose levels (Fig. 3). This result has been maintained up to the present, and the patient is insulin-free.

Despite this good result, some details of the case must be pointed out, since there are some differences from those reported in the literature. The first involves the indication. In fact, our patient was affected by insulin-treated type II diabetes, in which the islets' function was exhausted, as demonstrated by the very low pretransplant C-peptide level, without any response to the OGTT. This indication may be subject to criticism because the post-transplant islet function may have been due to the remaining activity of the endogenous cells. Moreover, the high discrepancy between the pre- and post-transplant results would seem to suggest good activity of the graft.

Another fact to consider is that the result was obtained despite a rejection episode, which required standard dosage steroid treatment, and a serious episode of sepsis. According to the literature, these two facts should account for compromised activity of the engrafted islets [2, 3, 5, 6, 9, 12].

Moreover, the number of islets transplanted would seem to be insufficient to obtain a good glycemic control, as described by other authors [1, 2, 10,11]. In fact, the C-peptide curve obtained after the OGTT in our patient presented the anomalies already reported by Alejandro et al. [2], with the absence of a first phase response and a delayed peak. On the basis of the experimental results and the similarity with patients studied before the development of type I diabetes, these anomalies were attributed to an inadequate number of functioning transplanted islets.

The good result, obtained despite these negative considerations, may be explained by the indication for transplantation. It is likely that the transplantation of even a small number of functioning islets may be sufficient to obtain euglycemic condition, even in the presence of unfavorable factors, by removing cirrhosis as a cause of diabetes.

Our experience confirms the feasibility of islet cell transplantation. More studies on the methods used to isolate, purify, and preserve islets, as well as on the best implantation site, may lead to an improvement in the results. A better understanding of the modification of the islets' function may lead to a better selection of candidates for combined islet and liver transplantation.

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