A Post–Liver Transplant Girl With Recurrent Cramps in the Legs

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Case Report

A 17-year-old girl was diagnosed with liver dysfunction during a regular medical follow-up for a previous liver transplantation. She had undergone the Kasai procedure (hepatoportoenterostomy) on the 73rd day after birth for biliary atresia, followed by living-donor liver transplantation from her father at 12 years of age because of liver cirrhosis associated with gigantic focal nodular hyperplasia. Although she had been well controlled on a maintenance dose of tacrolimus alone (1 mg/day), treatment with tacrolimus had been discontinued on her own judgment. A laboratory examination showed serum aspartate aminotransferase levels of 747 IU/L and alanine aminotransferase levels of 994 IU/L. She was clinically diagnosed as having an acute rejection reaction and was admitted to our hospital. Her liver function recovered by 1 g methylprednisolone pulse therapy, followed by oral prednisolone (PSL) and an increase in tacrolimus to 3.5 mg/day, with a monitoring therapeutic dose. Although both PSL and tacrolimus were gradually reduced to 10 mg/day and 2 mg/day, respectively, she first complained of recurrent cramps in the legs. In a few weeks she complained of being thirsty, polydipsia, and polyuria, even a month after the acute rejection reaction. She had no familial history of diabetes mellitus (DM) or was not obese. Laboratory findings were as follows: fasting blood sugar 29.6 mmol/L, HbA1c (hemoglobin A1c) 11.2%, immune reactive insulin 23.7 μU/mL, tacrolimus trough level 8.4 ng/mL. Her liver function, renal function, blood level of electrolytes, and blood gas assessment were all within normal ranges. A urinalysis showed severe glycosuria and was negative for ketone bodies.

Her initial therapy consisted of metformin (500 mg/day), a therapeutic diet (1800 kcal/day), and mycophenolate mofetil (500 mg/day) as a steroid-tacrolimus sparing agent, followed by a rapid reduction in steroid and maintenance of tacrolimus on a low therapeutic level (2 mg/day; Figure 1). Her symptoms disappeared within a month after the introduction of antidiabetic treatment. Her HbA1c levels gradually decreased to the normal range (<5.8%) within 4 months without acute or chronic rejection reactions. She no longer needed antidiabetic therapy 6 months from her initial treatment for DM. She is currently well and takes only low-dose tacrolimus (1 mg/day) with around 5 ng/mL as the target trough level without any recurrence of a rejection reaction or DM.

Discussion

A wide variety of immunosuppressants have clinically become available since the 1960s. With the improvement in survival rates, DM after transplantation, namely, posttransplant diabetes mellitus (PTDM), has been recognized as a major and serious complication and an independent risk factor for cardiovascular events, infections, and graft failure in donors who have been treated, particularly with tacrolimus (FK506).[1] The incidence of PTDM is 14% to 16% after solid organ transplantation.[2] More than half of the cases occur within a month after transplantation, with other cases occurring at a rate of 6% per year. The incidence of pediatric PTDM has increased significantly with time and has reached 20% in the period from 1996 to 1999.[3] Similar to type 2 DM, PTDM usually develops slowly, and the occurrence of diabetic ketoacidosis is rare. Following diagnosis, the levels of immunosuppressants are reduced or exchanged with hypoglycemic agents, including insulin therapy.

Tacrolimus, a calcineurin inhibitor, is a potent immunosuppressive agent and a promising agent for use in the management of posttransplant patients. Long-term patient and graft survival rates in children after organ transplantation are excellent under tacrolimus immunosuppression. However, possible diabetogenic effects, which seem to be associated with apoptosis induced in β cells, have been reported.[4] Tacrolimus impairs insulin

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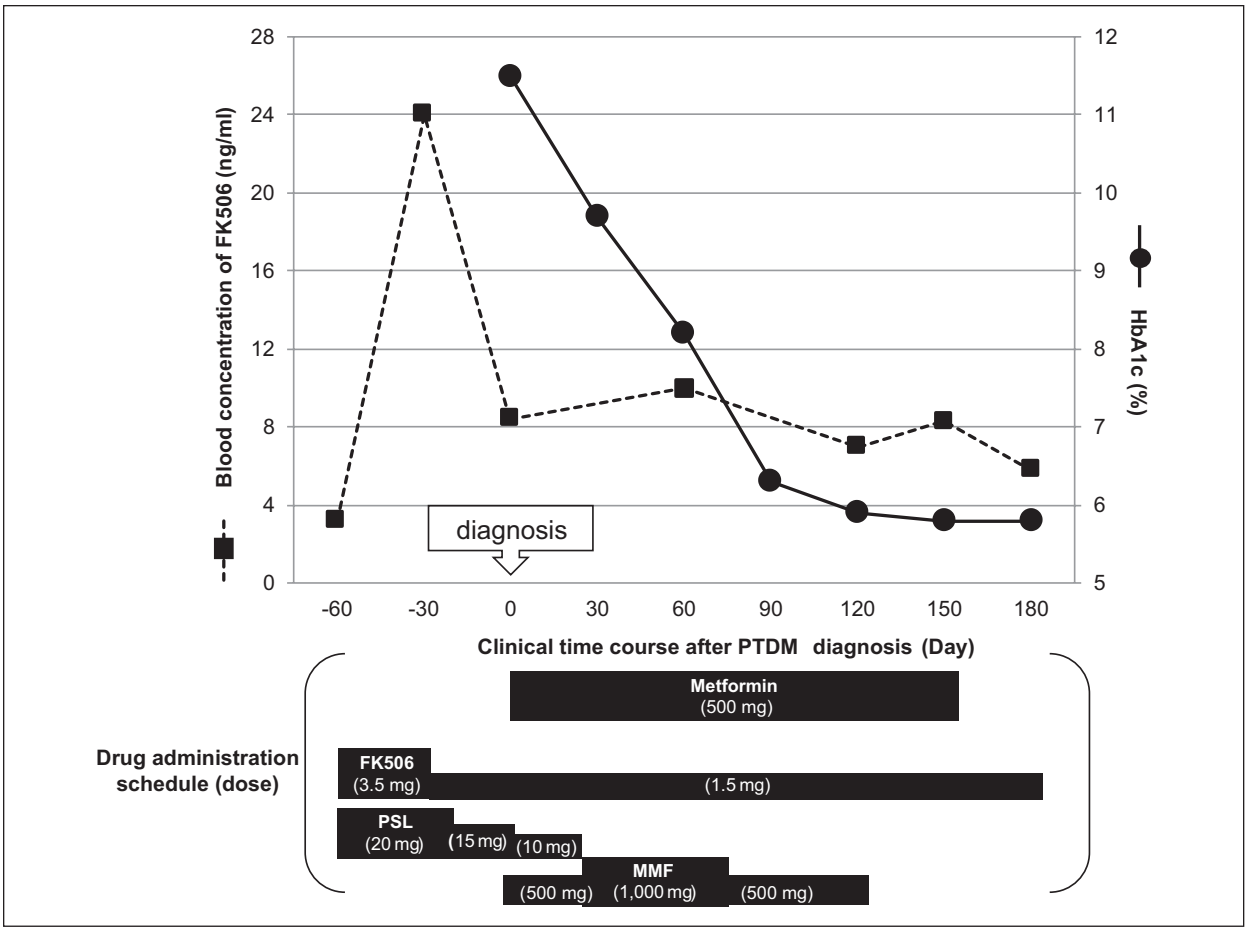

Figure 1. Clinical course

secretion at multiple steps in stimulus-secretion coupling, depending on the time and dose.[5] The reason why some subjects suffer from permanent DM and the others suffer from transient DM remains unclear. At the same time, steroids are well-known antagonists of the action of insulin, acting mainly in peripheral tissues. The issue of whether the diabetogenic effects of calcineurin inhibitors and steroids are independent, additive, or synergistic is currently unknown.

The first acute rejection reaction occurred during the long-term follow-up period due to her stopping regular medication. She needed to take immunosuppressants, including high doses of steroids and increased tacrolimus again, which resulted in the development of PTDM. We concluded that there was little association between liver damage and DM onset, because she was asymptomatic during the acute rejection reaction and her liver function surrogating markers, such as serum albumin, cholinesterase, bilirubin, and ammonia levels except for aminotransferase levels, were consistently within the normal range.

Cramps in the legs are known as a sign of dehydration, electrolyte imbalance, or neuromuscular disorders. DM possibly complicates all of these. In our case, recurrent cramps in her legs without any evidence of abnormal mineral balance and neuromuscular complications antecedently implied DM rather than other common diabetic symptoms such as polydipsia, being thirsty, or polyuria. She appeared to be relatively dehydrated in her hyperglycemic state and suffered from recurrent cramps. Children under immunosuppression often suffer from various general complaints due to their autoimmunity disorders or many drugs, so it would be wise to pay more attention to their complaints for the earlier detection of illness.

Her laboratory findings eventually showed relatively higher fasting glucose levels than insulin, even in her condition of glucose toxicity. This might suggest that her impaired insulin secretion was mainly due to exposed glucotoxicity, although it was possibly induced by pancreatic β cell damage after the tacrolimus treatment. Glucotoxicity leads to transiently impaired insulin

secretion, and insulin therapy efficiently rescues pancreatic β cell from glucotoxicity. We concluded that glucotoxicity induced the impairment of her insulin secretion when her insulin resistance got worse due to steroids.

In another case involving a Japanese adolescent, it was reported that a 14-year-old boy presented complications of PTDM as late as 200 days after hematopoietic stem cell transplantation due to the accumulation of immunosuppressants for the treatment of a chronic rejection reaction.[6] The authors concluded that tacrolimus rather than the steroid was likely to have contributed to the onset of DM, because of a shortage of intrinsic basal insulin secretion (urinary c-peptide 27.2 μg/day). However, diabetes appeared immediately after the readministration of high doses of steroids with a low maintenance dose of tacrolimus, with glucotoxicity (HbA1c 12.2%), suggesting that the steroid was the candidate for inducing PTDM like our case. The issue of whether there might be a difference in PTDM onset between solid organ transplantation and hematopoietic stem cell transplantation remains uncertain.

We succeeded in controlling blood glucose levels by oral diabetic therapies as an outpatient; however, we would have been able to manage her glycemic control with insulin on admission if she had been more seriously ill. Recent topics related to pediatric transplantation include strategies for minimizing the use of steroids, which affect not only glycemic control but also the growth and the cardiovascular system in children. To target diseased cells, many researchers have developed drug-delivery systems for specific cells, tissues, and even intracellular organelles.[7,8] In the future, such techniques have the potential for helping posttransplant children who require immunosuppression live without DM if it can be used as a drug-delivery system for preventing immunosuppressants from insulting pancreatic β cells.

Conclusion

Glycemic metabolism should be monitored in cases of posttransplant children, especially subjects who are taking tacrolimus, which has diabetogenic effects. More pediatric recipients could be protected from complications associated with PTDM by taking precautions, early interventions, and new therapeutic strategies, given the current prevalence of pediatric organ transplantations.

We should consider PTDM when posttransplant children recurrently suffer from cramps with the legs, regardless of follow-up periods or kinds of immunosuppressants.

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Declaration of Conflicting Interests

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