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Graft pancreatitis and hemorrhagic cystitis

Treatment with bladder irrigation and protease inhibition

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The absence of protease activators in the urinary tract is the physiological basis for the models of pancreas transplantation with exocrine drainage to the urinary bladder. The pancreatic proteases are secreted as inactive proenzymes, and they cause no harm to the mucous membranes of the bladder and urethra as long as they remain in this inactive form. Activated trypsin molecules, however, can start a cascade of autoactivation that also activates the other proteases. Moreover, the urinary epithelium has no natural resistance to these aggressive enzymes, and an activation causes an intense inflammatory reaction. Graft pancreatitis with hemorrhagic cystitis is an uncommon but serious complication after pancreas transplantation with exocrine drainage to the urinary bladder. Reoperation with enteric diversion has been reported to be necessary for management of the activated enzymes in the pancreatic secretion [3]. This complication, however, can be successfully treated in a conservative way, as illustrated in one of our patients with a pancreas graft.

A 34-year-old male patient with juvenile diabetes mellitus received a combined segmental pancreas and kidney graft from a cadaveric donor in April 1986. The surgical technique for the pancreaticocystostomy has been described earlier [1]. For immunosuppression, a combination of cyclosporin A, azathioprine, and prednisolone was used. In addition, prophylactic rabbit antithymocyte globulin (RATG, Fresenius, Bad Homburg, FRG) was given for the first 6 postoperative days. An indwelling bladder catheter was used for 10 days, and prophylactic anticoagulant treatment was given for 6 months [2].

There was an immediate onset of function of both grafts. The fasting blood-glucose level was normal after transplantation and no further insulin treatment was needed. The 24-h amylase output in the urine was about 6,000 μkat (microkatal) after 1 week. It rose further to about 10,000 μkat after 3 months and then remained at that high level. The S-creatinine level declined to 125 μmol/l after 1 week. A protracted, biopsy-verified, cellular rejection was treated in weeks 2-5 with methylprednisolone in bolus doses, RATG, and methylprednisolone in sequence. Finally, a CMV infection was treated with foscarnet (ASTRA, Södertälje, Sweden) for 16 days. These complications seemed to have no influence on the pancreatic function, which remained excellent.

At the 1-year follow-up, the function of both grafts was still excellent. S-creatinine was 150 μmol/l and the fasting blood-glucose level was normal. The 24-h urinary amylase output was around 10,000 μkat. At cystoscopy a normal bladder mucosa was observed and the pancreatic duct could be identified. Two weeks later the patient suddenly developed burning pain, urgency, and hematuria. The S-amylase level increased 20-fold and the urinary amylase output decreased to one-half. The S-creatinine was elevated to 180 μmol/l.

Repeated urinary cultures were negative. Sonography revealed a swollen pancreatic graft and a dilated renal pelvis. The swollen bladder mucosa was interpreted as a cause of the urinary outflow obstruction. Sonography of the native pancreas was normal and the fasting blood-glucose level remained normal.

Treatment was started with 500 mg cefadroxil three times daily for 5 days. During this time, hematuria, urgency, and grafted organ dysfunction progressed. A total dose of 375 mg methylprednisolone was given for 3 days as an anti-inflammatory treat-

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ment. Protease activation was suspected and oral feeding was replaced by i.v. nutrition. Continuous irrigation of the bladder with saline and the protease inhibitor aprotinin (Trasylol, Bayer, Leverkusen, FRG: 10,000 kallikrein IU/ml; 10 ml/3 l saline) was performed via an indwelling bladder catheter. Twelve liters of this solution was used for the first 24 h; this was subsequently reduced to 6 l/24 h. During this therapy, the hematuria disappeared within a week and the S-creatinine normalized. The patient was discharged from the hospital in good condition 3 weeks after admittance. The S-amylase level slowly declined to normal during the following 6 months. The urinary amylase activity slowly increased during this same period. Sonography of the transplanted organs revealed a normal pancreas, while the renal pelvis was still slightly dilated. The endocrine pancreatic function was normal, as measured by fasting blood-glucose (4.3 mmol/l) and glycosylated hemoglobin (5.7%).

The etiology of the pancreatitis in this case is not clear, but a cystoscopic examination 2 weeks earlier may have triggered the problem, either by introducing some infectious agent or by causing a pressure-induced trauma with an inflammatory reaction of the pancreas graft. The repeated negative urinary cultures and the progression and aggravation of the clinical symptoms and laboratory findings during the initial cefadroxil therapy suggest a chemical, rather than an infectious, etiology of the hemorrhagic cystitis. The favorable response to anti-inflammatory and antiprotease therapy further supports this interpretation. We conclude that bladder irrigation with saline and aprotinin is a simple, active, and conservative method of treatment for protease-induced hemorrhagic cystitis caused by graft pancreatitis.

References

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