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Solitary pancreas transplantation for life-threatening allergy to human insulin*

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Summary

We report on a 30-year-old man, with type 1 diabetes mellitus, who developed generalized allergy to insulin consisting of several bouts of tremor, tachycardia, breathlessness and syncope. Strong positive reactions to protamine and metacresol were demonstrated by skin-prick testing. Symptoms persisted despite the use of antihistamine therapy, Actrapid HM Paraben® and Monotard® (insulin without protamine and metacresol) and immunosuppression (tacrolimus). He underwent a cadaver pancreas transplantation with portal-enteric drainage in June 2003. Following the antithymocyte globulin induction, immunosuppression consisted in tacrolimus and sirolimus without steroids. The patient subsequently reported a complete resolution of his symptoms and excellent glycaemic control. Thirteen months after transplantation, the patient developed oral ulcerations and severe leucopoenia initially attributed to sirolimus, which was subsequently stopped. A hyperglycaemic episode following corticosteroid therapy for acute rejection therapy required the reintroduction of insulin. Allergic manifestations reappeared promptly. Currently, 2 years after transplantation, the patient is euglycaemic without insulin (glycated haemoglobin 5.8%) and he is free of allergic reactions.

Introduction

Hypersensitivity reactions to insulin preparations, particularly systemic allergy, are quite rare and pose a difficult dilemma for the management of insulin-dependent diabetic patients. Those reactions are reported in <1% of the whole diabetic population [1,2]. Allergic reactions to insulin could be either local (15–55% of cases from which only 5–15% require a treatment) or systemic (0.1–2%) [3,4]. Burning, erythema, pruritus, urticaria, induration and pain at the injection sites are the most common manifestations of local allergy. By contrast, the systemic manifestations of allergy to insulin are broad and vary from urticaria, bronchospasm to anaphylactic reactions and serum sickness disease with arthralgia, myalgia, headaches, fever and gastro-intestinal symptoms [5–7]. Three mechanisms are involved to explain the local reactions [3,6,8]: degranulation of mast cells in the presence of specific IgE directed against insulin; formation of antigen–antibody (IgG) complexes and complement fixation; delayed hypersensitization with lymphokines release. The most likely explanation for systemic allergy is the development of an immunization against insulin excipients, most often, protamine or metacresol or against insulin itself. Systemic reactions involve

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IgE and specific IgG. For the protamine allergy, several mechanisms have been suspected [3,9] including IgE antibodies formation, appearance of protamine–heparine complexes, mast cells degranulation and idiosyncratic reactions. Insulin allergy is also increased by exposure to exogenous insulins, mainly bovine insulins [7,8].

We report here the case of a young type 1 diabetic patient who presented life-threatening allergic reactions to two insulin excipients, i.e. protamine and metacresol. The implantation of a vascularized solitary cadaver pancreas successfully cured him.

Case report

A 29-year-old man, working in a paper factory had a past history of type 1 diabetes at the age of 15. C-peptide level was 0.07 pmol/ml, with positive islet cell antibodies (ICA) and anti-IA2 antibodies. He was treated by injections of biosynthetic human insulin 4 times a day [70–75 U/day, glycated haemoglobin (HbA1c) 8.0%]. Body mass index was 26.7 kg/m^2 and body surface area 1.88 m^2. Renal function was normal without proteinuria, and there was a stable mild diabetic retinopathy and neuropathy, but no microangiopathy. Since 1999, he presented with malaise, tremor, tachycardia, burning sensation, nervosism, visual troubles and dizziness. Hypoglycaemic events were excluded. This symptomatology occurred few minutes after each exogenous insulin administration and resumed 4–5 h later.

In 2002, malaises became frequent and were most often seen after each Actrapid® injections. The patient became breathless with short episodes of unconsciousness for which he had to quit his professional activities. Cutaneous reactions as well as drop in the blood pressure were never seen. Clinical symptomatology was not improved despite the use of antihistamine therapy. Psychiatric evaluation did not reveal any disorder. IgE and immune complexes were increased and allergic tests to insulin excipients were positive for protamine and metacresol. They were negative for paraben.

In September 2002, the patient was switched from Actrapid® to Insulin Paraben NovoNordisk® with HbA1c levels ranging between 7.2% and 7.7%. Because of recurrent life-threatening reactions, we proposed to the patient an immunosuppressive (IS) therapy and a pancreas transplantation with a solitary vascularized organ.

As for the immunological preparation, he received a HLA-DR semi-identical compatible blood transfusion along with tacrolimus aiming for serum trough levels between 5 and 10 ng/ml (IMX; Abbott Park, IL, USA). Despite the IS therapy, the patient did not report any improvement of his symptomatology.

Six months later, on June 22, 2003, he received a vascularized whole pancreas transplant, which was implanted on the right iliac vessels with the venous effluent drained into the portal system. The duodenal graft was anastomosed to the recipient bowel by a latero-lateral duodenojejunostomy.

The donor pancreas sharing 3 HLA antigens with the recipient was dispatched by the Eurotransplant organization.

Post-transplant IS therapy consisted in polyclonal antibodies preparation (R-ATG®; Fresenius-Biotech, Gräfelfing, Germany) as induction therapy at a dose of 4 mg/kg/day during 4 days, tacrolimus (Prograft®; Astellas; Brussels, Belgium) 0.2 mg/kg/day to reach serum trough levels between 8 and 12 ng/ml during the first 4 weeks and 5–10 ng/ml thereafter, and sirolimus (Rapamune®; Wyeth Pharmaceuticals, Lovain-La-Neuve, Belgium) 1–3 mg per day in order to maintain serum trough levels between 5 and 10 ng/ml. No steroids were given except for a 500 mg methylprednisolone bolus during the operative procedure.

Postoperative period was uneventful: exogenous insulin therapy was completely stopped on day 9 with normal glycaemic profiles and C-peptide levels. On postoperative month 2, a re-laparatomy was needed for adhesiolysis. The patient subsequently reported a complete resolution of his symptoms and excellent glycaemic control (HbA1c 6.1%) without rejection episode. Six months later, skin-prick tests remained positive for protamine alone. Thirteen months after transplantation, the patient developed oral ulcerations and severe leucopoenia that were initially attributed to sirolimus (white blood count: 1160/mm^3, neutrophils 2%, lymphocytes 66%, monocytes 24%, eosinophils 2%). Sirolimus was stopped but symptomatology did not improve. Fasting glucose deteriorated, and an acute rejection was suspected. Methylprednisolone 20 mg/day was given without benefit on white cell count. After corticosteroid therapy, hyperglycaemic episodes required the reintroduction of exogenous insulin for 5 weeks (55–60 U/day) and allergic manifestations promptly reappeared. Finally, considered as a potential toxic agent, atorvastatin was withdrawn and oral ulcers as well as leucopoenia disappeared. Sirolimus could be readministered,

Table 1. Homeostasis model assessment (HOMA 2) estimating insulin resistance (IR) β-cell function (% B) insulin sensitivity (% S) (10).

	Insulin resistance (IR)	β-cell function (%B)	Insulin sensitivity (%S)
June 2003, Month 1	1.0	71.7	102.1
December 2003, Month 6	0.8	65.9	129.7
July 2004, Year 1	2.0	87.9	49.1
May 2005, Year 2	1.0	59.2	104.3

prednisolone was progressively tapered and insulin therapy stopped.

Currently, 24 months after transplantation, all malaises, dizziness and other symptoms have completely disappeared. The patient is back to work and sustains a normal life, with a normal renal function, normal metabolic tests (HbA1c 5.8%), (Table 1) [10], and no lipid impairment. Current therapy includes tacrolimus, sirolimus, diltiazem and candesartan cilexetil. Allergic reactions are absent. Cutaneous screening is negative for metacresol but still positive for protamine.

Discussion

This 30-year-old man was successfully transplanted with a solitary 3 HLA antigen-matched vascularized pancreas transplant for life-threatening allergic reactions to insulin excipients. Two years later, he sustains a normal life and a full-time job under a tacrolimus-based IS therapy without steroids and with normal metabolic profiles. Our patient did not have atopic predisposition and he never received porcine insulin. Specific IgG and IgE dosages were not performed but anti-insulin antibodies could not be found. Skin tests were positive only for protamine and metacresol.

The therapeutic approach of patients with insulin allergy has been extensively explored. When a regression of local allergic reactions does not occur spontaneously or after a 2–4-week antihistaminic therapy, it is recommended to change the insulin type and to propose human insulin analogues [5,8,11,12]. That was totally unsuccessful in our patient. Then, modification of the injection material, multiple injection therapy, and injection sites modification can be proposed along with SC injection of 1 μg dexamethasone per unit of insulin [5,7,13]. In this context, Sola *et al.* [14] reported a type 1 diabetic patient with local allergic reactions successfully treated by a continuous sub-cutaneous insulin infusion. Finally, oral steroid therapy is also another alternative [5,6].

Tacrolimus therapy was started along with the pre-transplant blood transfusion; with the hope that IS therapy could have a beneficial effect on allergic manifestations. This was unfortunately not the case. Interestingly, 90–94% of the systemic allergies are sensitive to a desensitization treatment, which cannot be applied to unstable diabetes [8,15]. In our patient, gradual desensitization with low doses of insulin was indeed not appropriate because of the subject's insulin requirements and the risk of poor metabolic control. Vascularized pancreas transplantation is an alternative treatment of systemic insulin allergy. To date, prior to our patient, only one case had been reported in a type 1 diabetic woman with systemic allergy to insulin that was not improved by insulin type changing, desensitization treatment, steroids and cyclophosphamide therapies [16]. A solitary pancreas transplant was successfully performed using OKT3 induction and ciclosporin A, azathioprine and steroids as maintenance IS therapy. Allergic symptomatology disappeared after transplantation, which allowed a euglycaemic status. Vascularized pancreas transplantation could also be a therapeutic option for diabetic patients who develop insulin resistance because of inactivation of insulin at the subcutaneous level [17]. Finally, islet transplantation could also be a theoretical alternative therapy for insulin allergy. Indeed, islet transplantation technique is improving and is now providing insulin independence in 94% of the nonuraemic patients at 1 month. Long-term follow-up still, however, underlines a need for further progresses as insulin independence at 5 years is only 7.5% [18,19].

Post-transplant IS in our patient consisted of tacrolimus and sirolimus, without steroids, as reported by the Edmonton protocol and studies using tacrolimus in kidney and pancreas transplantation [18,20]. Unfortunately, our patient presented side effects firstly and wrongly attributed to sirolimus treatment that was withdrawn. On IS monotherapy, i.e. tacrolimus, he presented deterioration of the fasting glucose levels leading to the treatment of a suspected pancreas graft rejection episode. The need for insulin therapy after corticosteroid administration resuscitated allergic manifestations, whereas identified allergic components were not re-tested. This probably underlines a general hyper-reactivity status presented by our patient, even under corticosteroid treatment. The suppression of atorvastatin as the potential toxic agent permitted to oral ulcers and leucopoenia to resolve. Steroids could be reduced and then stopped as well as insulin therapy. Currently, 2 years later, the patient is enjoying an excellent quality of life, and has resumed a full-time job.

In conclusion, solitary vascularized pancreas transplantation is a valid therapeutic option for life-threatening systemic insulin allergic reactions.

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