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# Autoimmune Diabetes Recurrence After Pancreas Transplantation: Diagnosis, Management, and Literature Review

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Statistical Analysis C
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**Background:** Pancreas transplantation can be a viable treatment option for patients with type 1 diabetes mellitus (T1DM), especially for those who are candidates for kidney transplantation. T1DM may rarely recur after pancreas transplantation, causing the loss of pancreatic graft. The aim of this study was to describe the prevalence of T1DM recurrence after pancreas transplantation in our series.

**Material/Methods:** Eighty-one patients transplanted from 2002 to 2015 were included. Autoantibody testing (GADA and IA-2) was performed before pancreas transplantation and during the follow-up.

**Results:** The series includes 48 males and 33 females, mean age 37.4±5.7 years and mean duration of diabetes 25.5±6.5 years. Patients received simultaneous pancreas kidney (SPK) transplantation. After SPK transplantation, 56 patients retained pancreatic graft, 8 patients died, and 17 patients lost their pancreatic graft. T1DM recurrence occurred in 2 of the 81 transplanted patients, yielding a prevalence of 2.5%, with an average time of appearance of 3.3 years after transplant. Pancreatic enzymes were normal in the 2 patients, ruling out pancreatic rejection. T1DM recurrence was confirmed histologically, showing selective lymphoid infiltration of the pancreatic islets.

**Conclusions:** T1DM recurrence after pancreas transplantation is infrequent; however, it is one of the causes of pancreatic graft loss that should always be ruled out. Negative autoimmunity prior to transplantation does not ensure that T1DM does not recur.

**MeSH Keywords:** **Autoantibodies • Autoimmunity • Diabetes Mellitus, Type 1 • Immunosuppression • Pancreas Transplantation**

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## Background

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterized by the presence of a lymphocytic cellular infiltration of the pancreatic islets (called "insulitis") that causes a selective destruction of beta cells and loss of insulin secretion [1]. Cellular and humoral components are involved in T1DM pathogenesis. Cellular components are represented by circulating autoreactive memory T cells (CD4+ and CD8+) [2–4]. Humoral response includes circulating autoantibodies to islet cell autoantigen, such as anti-glutamic acid decarboxylase (GAD) [5], anti-tyrosine phosphatase (anti-IA2) [6], anti-insulin antibodies (IAA) [7], islet cell antibodies (ICA), and anti-cation efflux transporter Zn78 antibodies [8]. These autoantibodies are detected at the onset of the disease and, some years after endocrine pancreatic loss, persist or progressively decrease to become undetectable [9].

On the other hand, islet and whole pancreas transplantation are the only clinically established beta cell replacement treatments in patients with T1DM, achieving long-term normoglycemia in successful pancreas transplantation. Three types of whole pancreas transplantation can be performed: simultaneous pancreas kidney transplantation (SPK), pancreas after kidney transplantation (PAK), and pancreas transplantation alone (PTA) [10].

However, T1DM, as an autoimmune disease, can recur after pancreas transplantation. T1DM recurrence after pancreas transplantation is not a common complication [11,12] but generally leads to pancreatic graft loss despite rescue treatment.

Diagnosis of T1DM recurrence after pancreas transplantation includes clinical approach, islet cell autoantibody measurement, and pancreas graft biopsy [13]. The positivity of these autoantibodies may raise the suspicion of autoimmune diabetes, and the positivity of 2 or more autoantibodies is highly predictive of the development of T1DM [14]. Pancreas graft biopsy showing insulitis is the histological hallmark that leads to diagnostic confirmation [13].

The aim of this report is to describe the cases of T1DM recurrence in our cohort of patients undergoing pancreas transplantation and to carry out a literature review.

## Material and Methods

### Patients

This was a prospective study of 81 patients with T1DM who received SPK transplantation at University Hospital La Fe in Valencia (Spain) between 2002 and 2015.

Demographic, clinical, and biochemical data, including HbA1c, fasting C-peptide, fasting blood glucose, and autoantibodies, were collected. Serum amylase and lipase levels were monitored to aid in assessing pancreatic exocrine graft function and rejection.

### Transplantation procedure

#### *Surgical technique*

All pancreas transplantations were performed by the same surgical team at the same hospital between 2002 and 2015. All pancreatic and kidney grafts had been procured from deceased donors. Pancreatic graft was placed into the right iliac fossa with an enteric drainage of pancreatic exocrine secretion, and the kidney graft was placed into the left iliac fossa, both of them placed extraperitoneally.

#### *Immunosuppression*

Antithymocyte globulin or basiliximab was used for induction immunosuppression therapy. As maintenance immunosuppression therapy, patients are currently treated with a combination therapy, which consists of a calcineurin inhibitor (tacrolimus, administered at a dose required to reach plasma levels between 7 and 10 ng/mL during the first 6 months and subsequently from 5 to 8 ng/mL) and an antimetabolite (mycophenolate mofetil: dose 1000 mg twice per day) or mammalian target of rapamycin inhibitor (sirolimus). Additionally, steroids were used. Prednisone was the most frequently used steroid, with an initial daily dose of 20 mg, which was discontinued and finally withdrawn at 6–12 months after pancreas transplantation.

#### *Autoantibody testing*

Autoantibody testing was performed before pancreas transplantation and during the follow-up. Well-established enzyme-immunoassays (ELISA) were used to measure autoantibodies to the autoantigens GAD65 (GADA) and IA-2 (IA-2A), and indirect immunofluorescence was used to measure islet cell antibodies (ICA). GADA and IA-2A levels are expressed in U/mL. The upper limit of normal range for GADA and IA-2A antibodies was 4.99 and 14.99 U/mL, respectively. ICA levels are expressed as positive or negative values.

Insulin autoantibodies were not measured, as exogenous insulin treatment can induce positivity of antibodies against insulin, which might be indistinguishable from autoantibodies.

The technique to measure autoantibodies to the zinc transporter 8 (anti-Zn8) was not available in our hospital.





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### Acute rejection diagnosis

Acute pancreatic graft rejection was suspected when there was an increase in serum amylase levels and/or serum glucose levels together with an abrupt drop in C-peptide serum levels and/or abdominal pain occurred. Nevertheless, measurements of serum amylase and lipase tend to be relatively non-specific, and are thus generally not considered as reliable indices of rejection, or validation of non-rejection. For this reason, if acute pancreas rejection was suspected, the diagnosis was confirmed with pancreas graft biopsy.

Pancreas graft biopsy was obtained with a percutaneous needle biopsy technique. The pancreatic tail was the chosen area to perform the biopsy since it generally provides better histological support for T1DM recurrence as it has the highest density of islet cells. Biopsies were performed under local anesthesia and were guided by ultrasound.

### Ethics approval

This study was approved by Comité Ético de Investigacion Clínica (CEIC) of La Fe Health Research Institute, Valencia (Spain). This article contains human studies approved by CEIC. Written informed consent was obtained from all patients in this study.

## Results

This study included 81 patients with T1DM (48 males and 33 females, mean age 37.4±5.7 years, BMI 23.9±3.1 kg/m$^2$, mean duration of diabetes 25.5±6.5 years) who received SPK transplantation. All patients had no detectable C-peptide before transplantation.

Before pancreas transplantation, 15.8% of patients were positive for GADA and 7.3% were IA-2A-positive.

After SPK transplantation, 56 patients retained the pancreatic graft (42 of them with normofunctioning pancreas and 14 with low doses of insulin therapy), 8 patients died, and 17 patients lost their pancreatic graft. The causes of pancreatic graft loss were:

- Pancreas rejection in 7 patients. Increased amylase and lipase levels were found in all of the cases. Pancreas graft biopsy was made in 5 cases, confirming graft rejection. In the other 2 cases, kidney and pancreas graft rejection coexisted and only renal graft biopsy was performed.
- Explant due to surgical complications in 8 patients: graft venous thrombosis in 3 cases, enteric fistula in 2 cases, acute pancreatitis in 2 cases, and surgical suture dehiscence in another case.
- T1DM recurrence in 2 patients.

Three of the patients with pancreas graft loss for surgical complications or pancreas rejection after SPK underwent subsequent PAK. No patients with autoimmune diabetes recurrence were retransplanted.

T1DM recurrence was found in only 2 patients after SPK transplantation, yielding a prevalence of 2.5%. T1DM recurrence was the cause of pancreatic graft loss in 11.8% of cases.

Baseline characteristics of the 2 patients who developed a T1DM recurrence are included in Table 1.

Initially, after SPK transplantation, both patients maintained well-functioning pancreatic and renal grafts: achieved normoglycemia (their glycosylated hemoglobin levels became normal and presented normal levels of fasting C-peptide and normal fasting blood glucose), and were insulin- and dialysis-free, for 24 and 54 months, respectively.

However, classical diabetes symptoms with elevated fasting blood glucose and low C-peptide serum levels appeared at 24 and 54 months after transplant, requiring insulin therapy. Both patients returned to their pretransplant insulin requirements. Serum amylase and lipase levels were normal.

Metabolic data and immunosuppression schedule are summarized in Figures 1, 2.

A transgression in immunosuppression schedule was ruled out and tacrolimus plasma levels were kept within the established limits. Since both kidney grafts maintained good function, the immunosuppressive regimen was continued. There was no explant of the pancreatic grafts.

Concerning autoantibody follow-up, the 2 patients with T1DM recurrence presented negative values of GADA and IA-2A before SPK transplant. Only 1 patient converted GADA and IA-2A levels from negative pretransplant levels to positive at T1DM recurrence. In the other patient, only GADA became positive at the moment of T1DM recurrence, while IA-2A levels became positive 1 year later (Figure 3). Islet cell antibodies (ICA) were measured only in 1 patient after diabetes recurrence, not before SPK, being positive (titer 1/40).

Pancreas graft biopsy was performed in the 2 patients, showing an inflammatory T cell infiltrate targeting beta cells, called insulitis, sparing the exocrine tissue and confirming T1DM recurrence (Figure 4).





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**Table 1.** Baseline characteristics of 2 patients who developed T1DM recurrence after pancreas transplantation.

| | Patient n° 1 | Patient n° 2 |
|---|---|---|
| **Recipient characteristics** | | |
| Gender recipient | Female | Male |
| Recipient age at transplantation (years) | 31 | 33 |
| Duration of diabetes (years) | 22 | 20 |
| Type of dialysis program | Hemodialysis | Hemodialysis |
| Duration of dialysis program before pancreas transplantation (years) | 2 | 3 |
| HLA haplotypes | A*01<br>A*02<br>B*08<br>B*18<br>DRB1*03<br>DRB1*03<br>DQ*0201<br>DQ*02 | A*01<br>A*02<br>B*08<br>B*50<br>DR*3<br>DR*4 |
| **Donor characteristics** | | |
| Gender | Male | Female |
| Age (years) | 26 | 35 |
| Cause of death | Suffocation | Other |
| HLA haplotypes | A*29-<br>B*18-<br>DR*11<br>DR*52 | A*02<br>A*32<br>B*27<br>B*41<br>DR*03<br>DR*51 |
| **Transplant characteristics** | | |
| Type of pancreas transplantation | SPK | SPK |
| Transplantation year | 2009 | 2010 |
| Insulin- and dialysis-free period after SPK transplantation | Yes | Yes |
| Follow-up time after the transplantation until T1DM recurrence (months) | 54 | 24 |

SPK – simultaneous pancreas and kidney transplantation; HLA – human leukocyte antigen; T1DM – type 1 diabetes mellitus.

## Discussion

T1DM recurrence in pancreas transplant recipients is not a common condition, probably due to the fact that a conventional immunosuppression schedule controls autoimmunity [15]. T1DM recurrence was initially described by Sutherland et al. in 1986 [16,17]. The first 2 cases were described in highly compatible HLA donors with a minimized immunosuppression schedule. Later, different studies provided additional evidence that T1DM recurrence occurred in unrelated SPK transplant recipients despite being HLA-mismatched and with standard immunosuppression schedule [18–25].

These studies have shown a variable prevalence of T1DM recurrence. In a histopathological examination of 100 pancreatic grafts, no cases of T1DM recurrence were found among recipients of pancreas graft from deceased donors with full immunosuppression. Instead, 9 cases (9%) of T1DM recurrence were reported among recipients with living-related grafts and minimal immunosuppression [18]. Most recently, Burke et al. [26] and Vendrame et al. [11] reported a T1DM recurrence in 7–8% of patients undergoing SPK, and Pugliese et al. [12] found that recurrent diabetes explained 50% of the immunological failures observed, being an underestimated situation, and probably due to the fact that there is no therapeutic regimen that so far controls islet autoimmunity progression [26–28].





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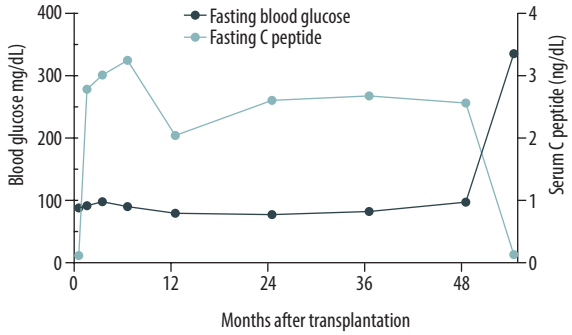
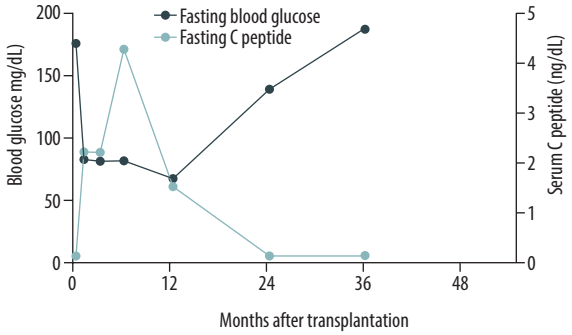



| Time after SPK (months) | 0 | 1 | 3 | 6 | 12 | 24 | 36 | 48 | 54 |
|---|---|---|---|---|---|---|---|---|---|
| HbA1c (%) | 8.4 | 6.4 | 5.5 | 5.4 | 5.1 | 5.3 | 4.9 | 5.0 | 11.2 |
| Insulin (UI/day) | 18 | 8 | 6 | 4 | 0 | 0 | 0 | 0 | 26 |
| Prednisone (mg/day) | – | 15 | 10 | 5 | 0 | 0 | 0 | 0 | 0 |
| MMF (mg/day) | – | 1500 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 |
| Tacrolimus (mg/day) | – | 8 | 5 | 8 | 11 | 9 | 5 | 5 | 5 |
| Tacrolimus blood levels (ng/mL) | – | 6 | 11 | 4 | 8 | 12 | 7 | 8.2 | 10.2 |

**Figure 1.** Long-term endocrine function after SPK of patient no. 1, who presented T1DM recurrence at 54 months after transplantation. Gray line represents fasting C-peptide (ng/mL) and black line represents fasting blood glucose levels (mg/dL). Glycosylated hemoglobin (HbA1c) (%), daily insulin requirements (UI/day), dairy prednisone, mycophenolate mofetil (MMF), and tacrolimus doses (mg/day) and blood level of tacrolimus (ng/mL) are indicated in the table below the graph.




| Time after SPK (months) | 0 | 1 | 3 | 6 | 12 | 24 | 36 |
|---|---|---|---|---|---|---|---|
| HbA1c (%) | 6.5 | 5.0 | 5.2 | 5.5 | 5.6 | 7.4 | 8.6 |
| Insulin (UI/day) | 28 | 12 | 12 | 0 | 0 | 10 | 20 |
| Prednisone (mg/day) | – | 15 | 10 | 8 | 5 | 0 | 0 |
| MMF (mg/day) | – | 1500 | 1000 | 1000 | 1000 | 1000 | 1000 |
| Tacrolimus (mg/day) | – | 5 | 5 | 2 | 2 | 4 | 5 |
| Tacrolimus blood levels (ng/mL) | – | 12 | 13 | 5 | 7 | 6 | 11.5 |

**Figure 2.** Long-term endocrine function after SPK of patient no. 2, who presented T1DM recurrence at 24 months after transplantation. Gray line represents fasting C-peptide (ng/mL) and black line represents fasting blood glucose levels (mg/dL). Glycosylated hemoglobin (HbA1c) (%), daily insulin requirements (UI/day), dairy prednisone, mycophenolate mofetil (MMF), and tacrolimus doses (mg/day) and blood level of tacrolimus (ng/mL) are indicated in the table below the graph.

We report 2 cases of recurrence of islet autoimmunity after SPK transplantation in our cohort of 81 patients, which represents a global prevalence of 2.5%. Our prevalence is lower than that described in the literature. This is probably due to the fact that our patient cohort is more recent and consequently had an improved immunosuppression regimen than the one described by Sibley [18].

The diagnosis of T1DM recurrence in our 2 patients was based on: (1) loss of insulin secretory function with sustained hyperglycemia that required exogenous insulin therapy; (2) seroconversion of autoantibodies at the moment of recurrence; (3) compatible pancreatic graft biopsy; and (4) absence of evidence of exocrine pancreas or kidney rejection (unchanged serum amylase and lipase levels). The presence of circulating autoreactive T cells (CD4 or CD8) around the time of diagnosis could not be determined because the technique required tetramer technology, which was not available in our hospital.

In our series, before pancreas transplantation, 15.8% and 7.3% of patients presented increased GADA and IA-2A values, respectively. These data are similar to those described by Martins et al. [13], who reported that 21.5% of patients were positive for GADA, 10.4% were ICA-positive, and 3% were IAA-positive before SPK transplantation, GADA being the most frequently positive autoimmune marker [13]. However, none of the patients who were positive for GADA and IA-2A before the transplant had a subsequent T1DM recurrence. Hence, pretransplant autoantibody positivity does not seem to predict future pancreas graft endocrine function or diabetes recurrence [13,22].

After SPK transplantation, pancreatic autoantibodies can persist, disappear, or reappear [9,12,22,29], and their pre-transplantation positivity does not influence pancreas graft survival [13]. The positivity of these autoantibodies is a good predictor of the appearance of autoimmune diabetes, and autoantibodies sometimes precede hyperglycemia by several





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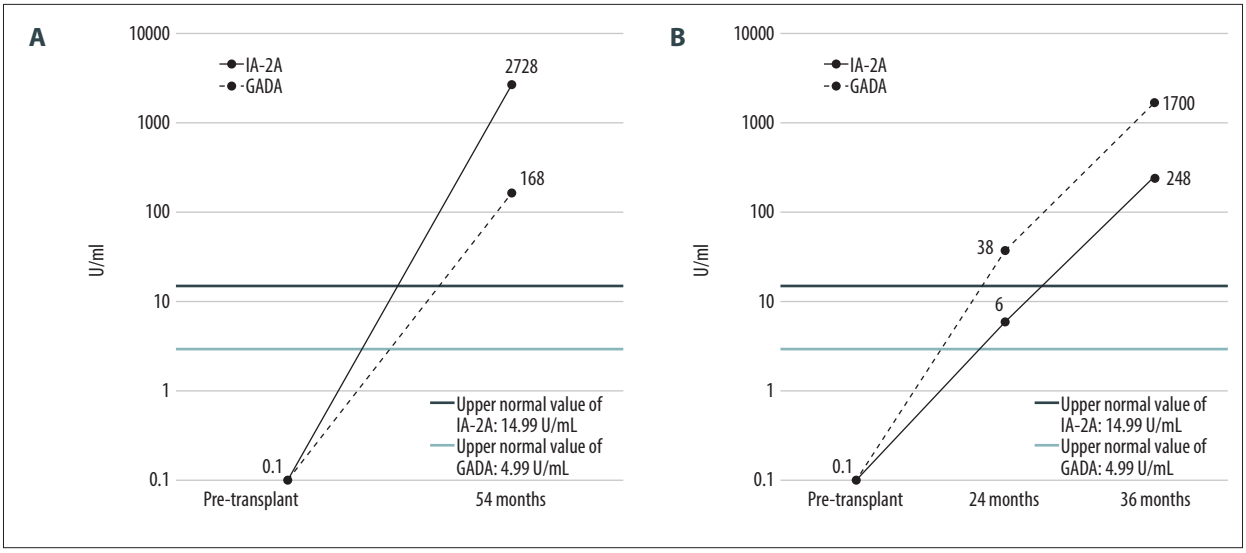


**Figure 3.** Follow-up of autoantibodies after SPK. GADA levels (U/mL) are represented as a dotted line and IA-2A levels (U/mL) as a continuous line. Gray and black line represent the upper limit of normal GADA (4.99 U/mL) and IA-2A (14.99 U/mL), respectively. (**A**) Follow-up of autoantibodies after SPK in patient no. 1. Before transplantation, GADA and IA-2A were negative, but at 54 months after transplantation both autoantibodies became positive (**B**) Follow-up of autoantibodies after SPK in patient no. 2. Before transplantation GADA and IA-2A were negative. After 24 months of SPK evolution, only GADA became positive, but 12 months later, IA-2A also had a positive conversion. SPK – Simultaneous Pancreas Kidney transplantation; GADA – autoantibodies to the autoantigen GAD65; IA-2A – autoantibodies to anti-tyrosine phosphatase.

months or years [27]. In the Miami study, subjects with autoimmune recurrence, increased by at least 2 autoantibodies, up to 70 times the upper limit of normal (ULN), appearing from 3 months to 3 years before diabetes recurrence [27] and after diabetes recurrence, pancreatic autoantibodies fluctuated along with T cell levels. For this reason, autoantibody values should be monitored routinely [13], especially GADA, which tends to be the most frequently positive one. When 2 or more autoantibodies become positive, the likelihood of autoimmune diabetes increases [14].

Nevertheless, in 2012, Assalino et al. [24] described 1 case of autoimmune recurrence after SPK transplantation in the absence of GADA and IA-2A. They suggested that pathogenesis of T1DM recurrence on a pancreatic graft is not a homogeneous phenomenon and that autoantibodies are not necessarily a cardinal feature of this condition.

In our sample, after SPK transplantation and coinciding with diabetes recurrence diagnosis, both patients presented a positivization of both autoantibodies – GADA and IA-2A. One patient increased GADA titers to 33 times the ULN and IA-2A titers to 182 times the ULN. The second one, increased GADA and IA-2A titers to 340 times the ULN and 17 times the ULN, respectively, at the moment of diabetes recurrence. The positivization of these 2 autoantibodies occurred despite receiving the correct immunosuppressive schedule. Levels of ZnT8 autoantibodies were not available. The inability to measure ZnT8 autoantibodies may have led to an underestimation of the development of recurrent autoimmunity, which is not assessed by GAD65 and IA2 measurements alone.

Although the positivization of these autoantibodies may lead to suspicion of the recurrence of autoimmune diabetes, pancreatic graft biopsy leads to confirmation of the diagnosis [13]. The histological hallmark is insulitis, which is a selective destruction of beta cells in the islets of Langerhans with preservation of alpha and delta cells and without signs of acute rejection (endovasculitis, diffuse parenchymal mononuclear cell infiltration, or both) or chronic vascular rejection (fibrous intimal proliferation in the arteries) [18,19,30].

In our study population, pancreas graft biopsy was performed in both patients due to strong suspicion of autoimmune diabetes recurrence. Pancreas graft biopsy showed insulitis (Figure 4), confirmed autoimmune diabetes recurrence, and helped to rule-out pancreas rejection. The results of pancreatic graft biopsy are similar to the cases of autoimmune diabetes recurrence described by other authors [18,19,30].

On the other hand, tacrolimus was used in all patients as part of immunosuppression maintenance schedule. Tacrolimus induces hyperglycemia due to direct toxicity on β-cells, reducing insulin production. In the absence of antibody testing or biopsy, it can mimic the condition of T1DM recurrence. In our series, tacrolimus toxicity was ruled out by biopsy [31].





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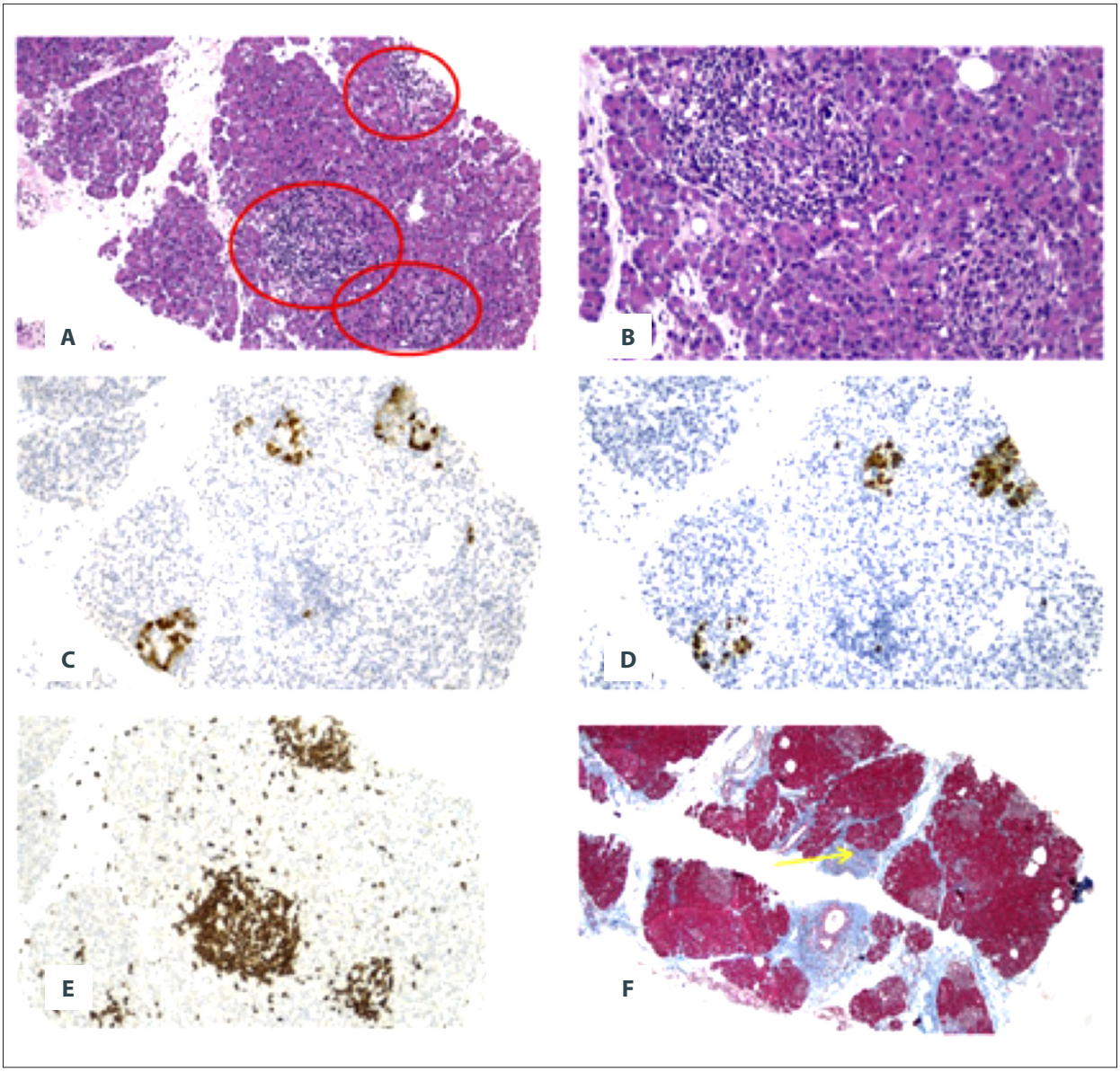


**Figure 4.** Photomicrographs of section of the pancreatic graft from Patient 1. Histopathology of the biopsy reveals early insulitis in Langerhans islets with marked islet atrophy, fibrosis, and severe beta cell depletion. There are no signs of acute rejection such as diffuse parenchymal mononuclear cell infiltration or endovasculitis, and there are no signs of chronic rejection such as necrosis, acinar atrophy, parenchymal fibrosis, and obliterative arteriopathy. C4d deposits are not present in vessels (antibody-mediated rejection). (**A**) (20×). Red circles show marked islet hyperplasia of 2 of the islets on a single lobe. (**B**) (40×). Reveals insulitis and islet cell hypertrophy. (**C**) (20×). Pseudoatrophic islet cells with glucagon staining positive for the presence of alpha cells. (**D**) (20 ×). Insulin staining, which identifies insulitis in 3 of the islets and residual beta cells. (**E**) Positive staining for CD3+ in accordance with lymphocytic infiltration of the 3 islets (insulitis). (**F**) (2×). Shows septal fibrosis.

At present, there is no treatment that alters the course to graft loss and T1DM recurrence. But sometimes, at the beginning of recurrence, there is a residual insulin secretion, and pancreas graft biopsy reveals the presence of insulin-positive islets. In these cases, it is justified to try immunotherapy to preserve insulin secretion. The Miami group treated autoimmune relapse with anti-lymphocyte (anti-B and/or anti T cell) therapies, with an initial improvement of pancreatic graft function in a few cases, but autoimmune activity recurred after a short time. After the second recurrence, the same clone of autoreactive GAD-specific T cells, which had been found in the first recurrence, was identified [12,27]. This led to think that immunosuppressive agents cannot prevent the immune response. On the other hand, other strategies have been





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developed targeting T cells (CD4 and CD8) to try to stop the progression of T1DM [32].

Recently, a team achieved the remission of autoimmune recurrence 6 years after SPK transplantation, using steroid boluses, plasmapheresis, and 2 infusions of rituximab, in addition to immunosuppression maintenance [33]. However, they did not test the autoreactivity of T cells, which could be a temporary remission. More follow-up time is required to confirm that autoimmune diabetes recurrence has been effectively treated.

In our sample, both patients with diabetes recurrence had no residual insulin secretion: fasting C-peptide and insulin serum levels were very low and pancreas graft biopsy showed a lack of insulin staining; therefore, we did not treat autoimmune diabetes recurrence. Both patients returned to their basal insulin therapy.

Finally, in our study population, diabetes recurrence was responsible for pancreatic graft loss in 11.8% of the cases. This percentage is higher than that described by Gruessner et al. [34,35], who analyzed the main causes of graft failure after pancreas transplantation. They concluded that, after the first-year after transplant, immunological graft loss was higher in solitary transplants, and diabetes recurrence only accounted for a small percentage (less than 2.5%) of graft losses. The difference between Gruessner's results and ours could be due to the difference in sample size: they analyzed a sample of more than 48 000 pancreas transplantations, while we only analyzed 81 transplantations.

To sum up, we describe the prevalence of diabetes recurrence after pancreas transplantation, patients' characteristics, and the follow-up of autoantibodies and glycemic values in a sample of 81 pancreas transplantations. We found some similarities with other series described in the literature. Our results confirm the fact that autoimmune diabetes may reappear after pancreas transplantation, even when autoimmunity was negative prior to transplantation. The main weakness of our series is that autoantibody measurement was performed after the onset of hyperglycemia, and was not routinely monitored.

## Conclusions

The prevalence of autoimmune diabetes recurrence after pancreas transplantation is infrequent, but it is one of the causes of pancreatic graft loss that should always be ruled out. Negative autoimmunity prior to transplantation does not ensure that autoimmune diabetes does not recur.

### Conflicts of interest

None.

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