



DR JOHN FUNG (Orcid ID : 0000-0002-3038-0441) DR PIOTR WITKOWSKI (Orcid ID : 0000-0002-4459-6673)

Article type : L - Letter to the Editor

Neither Amyloid Depositions nor Hepatic Steatosis are Associated with Marginal Islet Mass Early After Autotransplantation

To the Editor:

In 2008 Westermark et al. postulated that amyloid depositions found in allotransplanted islets derived from either islet overstimulation due to insulin production (as in type 2 diabetes), toxicity of immunosuppression, or perhaps both.¹ Amyloid depositions may promote a gradual decline in islet mass, progressive dysfunction, and ultimate failure.^{2,3} Herein, for the first time, we report the histopathological examination of an entire liver following autologous islet transplantation which sheds new light on the etiology of amyloid deposition in islet allografts.

A 38-year-old, non-diabetic male (BMI 34), with chronic pancreatitis and a heterozygous CFTR gene mutation (p.R553c.1657C>T) underwent a total pancreatectomy for intractable pain and simultaneous intraportal islet autotransplantation (TPIAT) to maintain endogenous insulin production. He received 152,000 islet equivalents suspended in 16 mL of tissue. Gross liver morphology and function were normal. Blood glucose levels were optimally controlled with ~17 units of insulin per day and HbA1c was 5.5% at one year. However, two years following TPIAT, the patient required liver transplantation due to decompensated alcohol-related liver failure. Histopathological examination of the explanted liver revealed 10% macrovesicular steatosis, severe steatohepatitis, and extensive bridging and sinusoidal fibrosis with numerous Mallory bodies and ballooned hepatocytes. Islets had preserved architecture and contained cells producing insulin, glucagon, pancreatic polypeptide, and somatostatin (Figure). Inflammatory cells were noted in portal tracts and fibrous septa but absent from the vicinity of the islets. Staining for amyloid and pancreatic acinar tissue was negative.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the <u>Version of Record</u>. Please cite this article as <u>doi:</u> 10.1111/ajt.16406

This article is protected by copyright. All rights reserved

Amyloid deposits in extracellular islet structures has been ascribed to islet allograft stress from chronic maximal insulin production^{1,2} However, we found no amyloid deposits on histopathological analysis despite a marginal transplanted islet mass (152K IEQ versus 1,000K IEQ found in normal individuals) and exposure to high metabolic demands related to end stage liver disease. Therefore, prior reports of peri-islet amyloid deposition may be related to other etiologies. A recent study in mice suggests toxicity form tacrolimus and rapamycin could be responsible .³

Overstimulation and exhaustion of marginal islet mass did not lead to amyloid deposition in this patient and thus suggests another explanation for islet dysfunction after autotransplantation.⁴ Islets were lodged in the terminal and lobular branches of the portal vein in a fashion similar to that seen in allotransplantation. Islets were dispersed relatively evenly in both lobes, which is consistent with blood flow patterns and islet infusion via the main portal vein. Despite cirrhosis and liver failure, the islets displayed preserved architecture and the usual hormone producing cells were present. In contrast to reports from allotransplantation, there was no particular pattern of steatosis near the islets.⁵ Macrovesicular steatosis was diffuse but localized to the regenerative nodules of the cirrhotic liver with no inflammatory cells in the vicinity of the islets, indicating a lack of allo- or auto-immune response in the islet allografts.

Islet grafts evaluated two years after marginal islet mass autotransplantation demonstrated neither amyloid depositions nor local hepatosteatosis. While the etiology remains unclear, this may indicate that toxic immunosuppression may be responsible for this phenomenon after islet allotransplantation.

> Gabriela S. Generette¹ Piotr J. Bachul¹ Katherine Boylan² Lindsay J. Yassan² John Hart² Jordan S. Pyda³ Jeffrey B. Matthews¹ John Fung¹ Piotr Witkowski¹

¹The Transplantation Institute, University of Chicago, Chicago, IL ²Department of Pathology, University of Chicago, Chicago, IL

This article is protected by copyright. All rights reserved

³ Department of Surgery, Beth Israel Deaconess Medical Center, Boston, MA

Correspondence Piotr Witkowski Email: pwitkowski@surgery.bsd.uchicago.edu

Acknowledgments

We acknowledge support from NIDDK P30DK020595 and the Kovler Family Fund.

Disclosure

20

Acce

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

References

- 1. Westermark GT, Westermark P, Berne C, Korsgren O. Widespread Amyloid Deposition in Transplanted Human Pancreatic Islets. N Engl J Med 2008;359(9):977–9.
- Westermark GT, Davalli AM, Secchi A, et al. Further Evidence for Amyloid Deposition in Clinical Pancreatic Islet Grafts. Transplantation 2012;93(2):219–23.
- 3. Dai C, Walker JT, Shostak A, et al. Tacrolimus- and sirolimus-induced human β cell dysfunction is reversible and preventable. *JCI Insight*. 2020;5(1).
- 4. Ali KF, San Martin VT, Walsh RM, et al. Change in Functional Beta Cell Capacity With Time Following Autologous Islet Transplantation. *Pancreas*. 2019;48(5):656-661.
- Jackson S, Mager DR, Bhargava R, et al. Long-term follow-up of hepatic ultrasound findings in subjects with magnetic resonance imaging defined hepatic steatosis following clinical islet transplantation. Islets 2013;5(1):16–21.

Supporting Information

Additional supporting information may be found online in the Supporting Section at the end of the article.

Figure Legend

Figure.

Hematoxylin and eosin stained sections of liver explant (Panel A) revealing a cirrhotic nodule with macrovesicular steatosis (left) and a large portal tract containing pancreatic islet cells in a portal vein branch (arrows). Panel B demonstrates pancreatic islet cells with associated capillaries within a portal vein branch. Immunohistochemical stains highlight the presence of hormone-producing pancreatic islet cells within portal vein branches, including glucagon (Panel C), insulin (Panel D), pancreatic polypeptide (Panel E), and somatostatin (Panel F). Scale bars correspond to 50 μm.

The majority of islet cell clusters were lodged in small terminal branches of the portal vein (diameter <100microns), with some present in larger branches (<200microns) in all segments of the liver. Overall, more clusters were found in the right portal branches (2.7% (0-8.8%)) compared to the left (1.1% (0-5%)) (p>0.05). The diameter of portal veins containing islet cells was on average 40µm (16-159). There were many islet cell clusters of synaptophysin positive cells found in terminal branches but none in sinusoids. Panel G presents patient glucose control and islet graft function. After TPIAT patient maintained stable islet graft function with good glucose control with A1c below 6.5% and stable fasting c-peptide levels; however, insulin requirements substantially increased when his liver function deteriorated (MELD 40).



Panel G

| Follow-up visit related to each Tx | Fasting glucose (mg/dL) | HbA1c (%) | Fasting c-peptide (pmol/mL) | MMTT stimulated c-peptide (peak) (pmol/mL) | Total average daily insulin (units) | Weight (kg) | Insulin IU/kg/day |
|--|-------------------------------|--------------|-----------------------------------|--|---|----------------|----------------------|
| pre TPIAT | 88 | 5.1 | 0.26 | 3 | 0.0 | 101 | 0.00 |
| Day 75 | 108 | 6.3 | 0.42 | 1.8 | 20.0 | 91 | 0.22 |
| 1 year | 95 | 5.5 | 0.22 | 1.5 | 17.3 | 104 | 0.17 |
| 2 years* | 105 | 5.7 | 0.33 | N/A | 81.0 | 107 | 0.76 |

*Patient with MELD 40 right before liver transplantation