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Original Article

Acute macular edema and peripapillary soft exudate after pancreas transplantation with accelerated progression of diabetic retinopathy

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Abstract

Background: The effect of pancreas transplantation on diabetic retinopathy remains inconclusive. Herein, we report six patients with type 1 diabetes mellitus (DM) who underwent pancreas transplantation and developed acute macular edema and peripapillary soft exudate with rapid progression to proliferative diabetic retinopathy.

Methods: In this retrospective observational study, diabetic patients who underwent pancreas transplantation in a single medical center and developed symptomatic acute macular edema and peripapillary soft exudate within 3 months after the operation were enrolled. The complete ophthalmic course and medical records of the patients were retrospectively reviewed. Diabetic retinopathy and progression following treatment after pancreas transplantation were measured.

Results: Six Chinese women with type 1 DM were enrolled in this study. Mean hemoglobin (Hb) A1c was 13.4% prior to transplantation and decreased rapidly to 6.5% within 2 months postsurgery. The patients had no or mild pretransplant diabetic retinopathy and developed acute symptomatic macular edema and peripapillary soft exudate in both eyes after pancreas transplantation. All macular edema resolved either with or without treatment. Five cases progressed to proliferative diabetic retinopathy and received panretinal photocoagulation. Diabetic retinopathy remained stable in all eyes after treatment, and the visual prognosis was good, except in one eye that had macular branch retinal artery occlusion with foveal involvement.

Conclusion: Acute macular edema after pancreas transplantation has a favorable treatment outcome despite rapid progression to proliferative diabetic retinopathy. High pretransplant HbA1c and abrupt blood sugar normalization may be related to the disease course.

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Keywords: diabetic retinopathy; hemoglobin A1c; macular edema; pancreas transplantation; soft exudate

1. Introduction

Pancreas transplantation is a potentially curative treatment to establish physiological normoglycemia in diabetic patients, particularly those with type 1 diabetic mellitus (DM).[1] Simultaneous pancreas and kidney transplantation (SPK) is the treatment of choice for diabetic patients with end-stage renal failure.[1] Pancreas transplantation is also performed

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after kidney transplantation to improve kidney survival and restore normoglycemia. With improvements in surgical techniques and immunosuppressive regimens, pancreas transplantation alone (PTA) is increasingly being performed in DM patients without advanced nephropathy.[2] It has been suggested that apart from achieving insulin-free euglycemia to improve quality and longevity of life, PTA before extensive microangiopathy may ameliorate or reverse diabetes-related complications.[3] According to the International Pancreas Transplant Registry, the number of SPK surgeries has remained stable since 1995, but the number of solitary pancreas transplants, including PTA, has quadrupled over the same period.[4]

The effect of pancreas transplantation on diabetic retinopathy remains inconclusive. Some studies have shown diabetic retinopathy improvement or stabilization after pancreas transplantation,[5,6] while others revealed no benefit or even reported disease progression.[7,8] It has been suggested that the pretransplant diabetic retinopathy status may be related to the progression of diabetic retinopathy after pancreas transplantation.[9–12] Other factors, such as pretransplant hemoglobin (Hb) A1c levels and DM duration may also affect the clinical course of diabetic retinopathy. In this study, we report a series of patients with no or mild nonproliferative diabetic retinopathy (NPDR) who underwent PTA and developed acute macular edema and peripapillary soft exudate within a few weeks, and progressed rapidly to proliferative diabetic retinopathy (PDR) within a few months. The complete clinical course and systemic data of these cases will be discussed to evaluate possible associated factors that may contribute to acute deterioration and progression of diabetic retinopathy after pancreas transplantation. To the best of our knowledge, this is the first case series discussing acute worsening of retinopathy after pancreas transplantation.

2. Methods

In this retrospective case series, we enrolled patients who had developed symptomatic acute macular edema and peripapillary soft exudate within 3 months after pancreas transplantation was performed in the Taipei Veterans General Hospital, Taipei, Taiwan, between September 2003 and May 2011. Six eligible patients were enrolled in the study; five patients were treated by one author (L.-I. Lau), and the other was treated by another author (A.-F. Li). Informed consent was obtained from all of the patients. Complete ophthalmic course and medical records were reviewed. This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital.

3. Results

Demographic profiles of the six patients are summarized in Table 1; all patients were young Chinese women who suffered from type 1 DM. The mean duration of DM prior to transplantation was 9.8 years (range, 6–15 years). Three patients were active smokers, but no patient had elevated blood pressure before or after the transplantation. Two patients (Cases 1 and 3) had elevated cholesterol before transplantation, which normalized after PTA. PTA was indicated in all patients because of poor glycemic control with frequent life-threatening hypoglycemia or hyperglycemia with preserved renal function. Pancreas transplantation was performed with systemic venous drainage through the inferior vena cava and enteric exocrine drainage in all patients. Postoperative immunosuppressants, including mycophenolic acid (Myfortic; Novartis AG, Basel, Switzerland) or mycophenolate mofetil (Cellcept, F; Hoffman-La Roche Ltd., Basel, Switzerland), tacrolimus (Porgraf; Astellas Pharma US, Inc., Northbrook, IL, USA), and oral prednisolone, were prescribed. Prednisolone was tapered gradually within 2–3 months. Two patients showed elevated serum amylase and lipase during the early postoperative period (Cases 1 and 6). Case 1 was diagnosed with acute graft rejection and was rescued successfully using methylprednisolone and thymoglobulin therapy, while Case 6 recovered spontaneously. Case 4 had pancreas graft atrophy at 8 months after transplantation and required insulin therapy. The mean HbA1c was 13.4% (range, 10.9–16.2%) prior to transplantation and decreased rapidly to 6.5% (range, 5.5–7.4%), with an average reduction of 6.9% (range, 5.3–9.4%) within 2 months (Fig. 1).

The ophthalmic courses of all of the patients are summarized in Table 2. The average interval from transplantation to subjective visual blurring was 5.8 weeks (range, 2–10 weeks). All patients complained of misty visual blurring despite a wide range of presenting best-corrected visual acuity (BCVA) from 6/6 to 6/30. Fundus examination revealed macular edema and peripapillary soft exudate (Figs. 2A, 3A, and 4B). Fluorescein angiography (FAG) showed peripapillary arteriole

Table 1
Demographics and medical data of the patients.

Case	Age (y)/sex	Smoking	DM duration (y)	Baseline HbA1c (%)	Baseline CCr (mL/min)	Baseline/2 mo Chol (mg/dL)	Serum amylase/lipase[a] (U/L)	SBP (mmHg)	Graft rejection[b]
1	31/F	+	9	10.9	91.07	245/182	325/1019	104	+, 20 d, suppressed
2	27/F	–	15	11.2	158.67	205/164	128/237	116	+, 19 mo, suppressed
3	22/F	+	6	15.0	94.03	265/194	121/148	113	–
4	22/F	–	6	16.2	144.88	196/180	171/159	112	+, 8 mon, atrophy
5	25/F	+	14	14.0	84.11	176/147	214/295	121	–
6	23/F	–	9	13.0	73.61	157/169	562/300	110	–

CCr = creatinine clearance rate; Chol = cholesterol; DM = diabetes mellitus; F = female; HbA1c = hemoglobin A1c; SBP = systolic blood pressure.
[a] Highest serum amylase/lipase level after transplantation before acute macular edema.
[b] Time to graft rejection and its outcome.

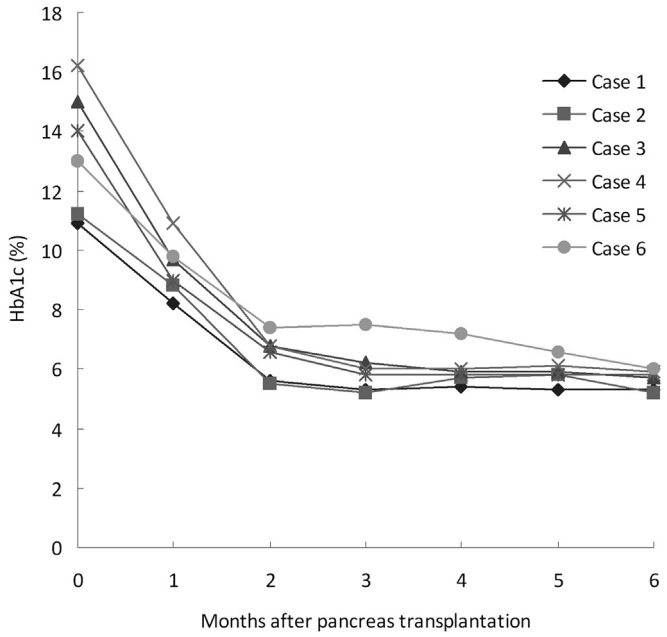

Fig. 1. The change in HbA1c during the first 6 months after pancreas transplantation. HbA1c decreased dramatically in the first two months after operation in each case. HbA1c = Hemoglobin A1c.

occlusion, intraretinal microangiopathy (IRMA), and diffuse vascular leakage at the macula without significant peripheral microangiopathy (Figs. 2B, 3B, and 3C). Three patients (Cases 3, 5, and 6) received intravitreal bevacizumab injection (IVB; 2.5 mg/0.1 mL) to treat macular edema, and one of them (Case 3) received concurrent panretinal photocoagulation (PRP), while one (Case 6) received PRP 3 weeks after IVB. Macular edema resolved spontaneously in three patients (Cases 1, 2, and 4) within 6 months. Peripheral microangiopathy with capillary nonperfusion evolved rapidly during the follow-up period (Fig. 3F) despite resolution of macular edema in all cases except Case 3, who received dense PRP during the initial treatment. Five cases progressed to PDR within an average of 7.4 months (range, 5–10 months), including Case 6, who received scattered PRP during the initial treatment. All patients received PRP, and two (Cases 2 and 5) progressed to vitreous hemorrhage and required supplementary PRP. Case 5 experienced branch retinal artery occlusion with foveal involvement in the right eye, and vision decreased to counting fingers. Case 3 experienced persistent cystoid macular edema in the left eye and received seven additional IVBs before the edema resolved 16 months later. The diabetic retinopathy remained stable in all eyes during the mean follow-up period of 31.3 months (range, 16–56 months).

3.1. Case reports

3.1.1. Case 1

A 31-year-old Chinese woman diagnosed with type 1 DM at 22 years of age underwent PTA due to multiple episodes of life-threatening diabetic ketoacidosis. She was an active smoker, and her preoperative HbA1c was 10.9%. She had normal renal function without nephropathy prior to transplantation. She experienced an episode of acute graft rejection with elevated amylase and lipase at 20 days after transplantation, which was controlled with methylprednisolone pulse therapy and thymoglobulin treatment. HbA1c decreased rapidly to 5.6% within 2 months after pancreas transplantation.

BCVA before transplantation was 6/6 in both eyes. Preoperative fundus examination revealed very mild NPDR in the left eye and only a few dots of hemorrhage. Subjective bilateral misty visual blurring was noted at 1 month after PTA. The presenting BCVA was 6/7.5 in the right eye and 6/6 in the left eye. The anterior segment was normal. Dilated fundus examination revealed multiple peripapillary soft exudates and macular edema in both eyes (Fig. 2A). FAG showed dilated vessels and numerous microaneurysms at the posterior pole, with profound late leakage in both eyes without peripheral microangiopathy or neovascularization (Fig. 2B). Optical

Table 2
Ophthalmic course of the patients.

Case	DR before PT	Onset[a] (mo)	Initial BCVA[b]	Initial therapy	Late DR	Time to PDR[c] (mo)	Other events	Follow-up (mo)	Final BCVA[b]
1	Mild NPDR OS	1	6/7.5, 6/6	—	PDR OU	8	—	17	6/6, 6/6
2	Mild NPDR OU	0.5	6/20, 6/20	—	PDR OU	7	VH OS ERM OU	20	6/10, 6/10
3	No DR OU	2.5	6/12, 6/20	IVB OS PRP OU	Severe NPDR OU	—	Persistent CME OS	38	6/6, 6/7.5
4	Mild NPDR OU	1.5	6/30, 6/30	—	PDR OU	7	—	41	6/7.5, 6/8.6
5	No DR OU	0.75	6/15, 6/15	IVB OU	PDR OU	5	VH OD BRAO OD	56	CF, 6/7.5
6	No DR OU	2.5	6/10, 6/20	IVB OU PRP OU	PDR OU	10	—	16	6/6.7, 6/6

BCVA = best-corrected visual acuity; BRAO = branch retinal artery occlusion; CF = counting fingers; CME = cystoid macular edema; DR = diabetic retinopathy; ERM = epiretinal membrane; IVB = intravitreal injection of bevacizumab; NPDR = nonproliferative diabetic retinopathy; OD = oculus dexter, right eye; OS = oculus sinister, left eye; OU = oculi uterque, both eyes; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; PT = pancreas transplantation; VH = vitreous hemorrhage.

[a] Interval from pancreas transplantation to acute worsening of diabetic retinopathy.

[b] Best corrected visual acuity of the right eye and the left eye.

[c] Interval from pancreas transplantation to development of proliferative diabetic retinopathy.

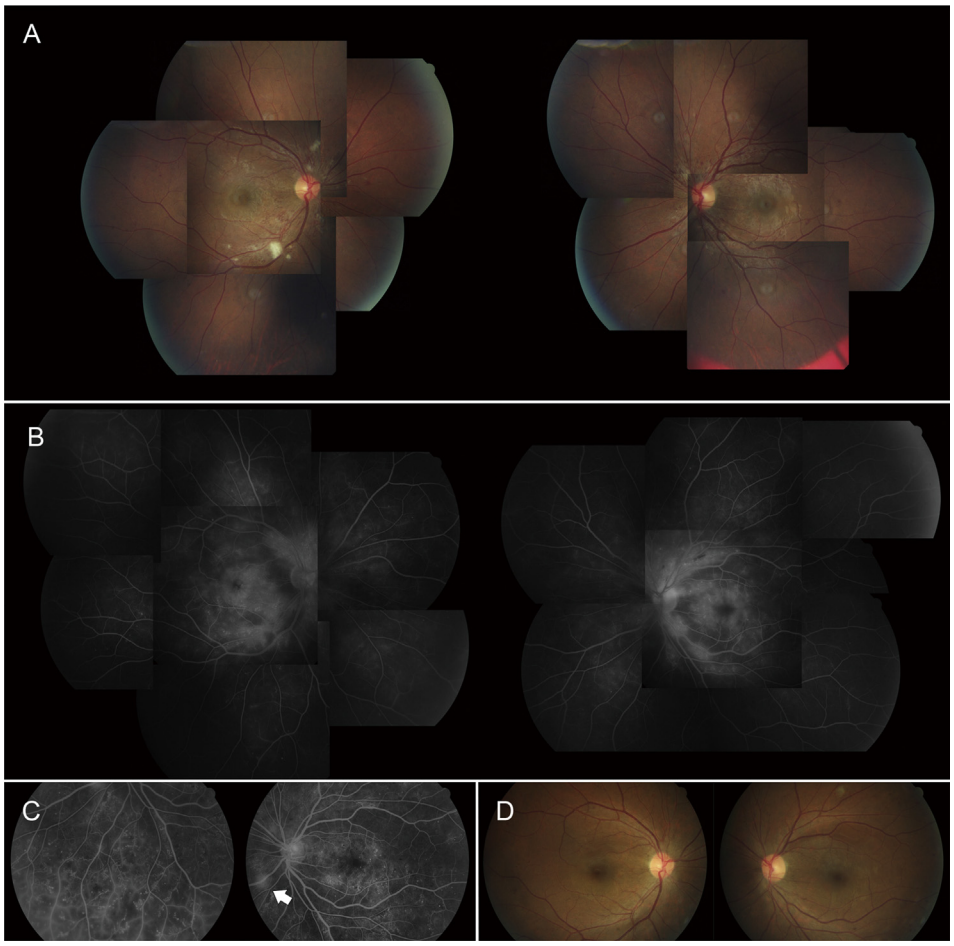

Fig. 2. Retina of Case 1 after pancreas transplantation (PT). (A) One month after PT, both eyes presented with macular edema and soft exudate without peripheral hemorrhage. (B) Fluorescein angiography revealed diffuse vascular leakage at the macula in late phase. (C) Eight months later, peripheral intraretinal microangiopathy and neovascularization (arrow) had evolved. Panretinal photocoagulation (PRP) was performed for both eyes. (D) The diabetic retinopathy regressed significantly after PRP and remained stable at 17 months' follow-up.

computer tomography (OCT) showed cystoid macular edema in the right eye. Autoimmune profiles were normal.

The macular edema resolved gradually within 2 months without any treatment, and the BCVA in the right eye improved to 6/5. However, peripheral dot and blot hemorrhage evolved 8 months after pancreas transplantation. FAG revealed a diffuse peripheral area of capillary nonperfusion in both eyes and new vessels elsewhere (NVE) in the left eye despite significant improvement in macular edema (Fig. 2C). PRP was thus performed in both eyes. The patient's condition remained stable, and BCVA was 6/6 in both eyes at 17 months after PTA (Fig. 2D).

3.1.2. Case 5

A 25-year-old Chinese woman diagnosed with type 1 DM at 11 years of age underwent PTA due to poor glycemic control. She was an active smoker, and her preoperative HbA1c was 14.0%. She had no amylase or lipase elevation, nor signs of graft rejection after transplantation. HbA1c dropped rapidly to 6.6% at 2 months and to 5.8% at 3 months after transplantation.

The patient had no known retinopathy before surgery. Visual blurring developed 3 weeks after surgery, at which time BCVA was 6/15 in both eyes. Fundus examination showed bilateral multiple peripapillary soft exudates and marked macular edema (Fig. 3A). FAG revealed a peripapillary focal capillary nonperfusion area, venous beading, and marked cystoid macular edema in both eyes (Figs. 3B and 3C). OCT showed cystoid macular edema with subretinal fluid in both eyes (Fig. 3D). IVB was performed in both eyes, and BCVA improved to 6/12 in the right eye and 6/7.5 in the left eye following cystoid macular edema resolution (Fig. 3E). Peripapillary IRMA and soft exudate failed to resolve, and PRP was performed in both eyes. Two months later, macular branch retinal artery occlusion occurred in the patient's right eye, and vision dropped to counting fingers (Fig. 3F). The occluded retinal vessels failed to recanalize despite antiplatelet, anticoagulant, and hyperbaric oxygen therapy. Retinopathy progressed with the development of new vessels on the optic disc and NVE were noted despite full PRP in both eyes (Fig. 3G). An episode of vitreous hemorrhage occurred in the patient's right eye during the follow-up period. Three

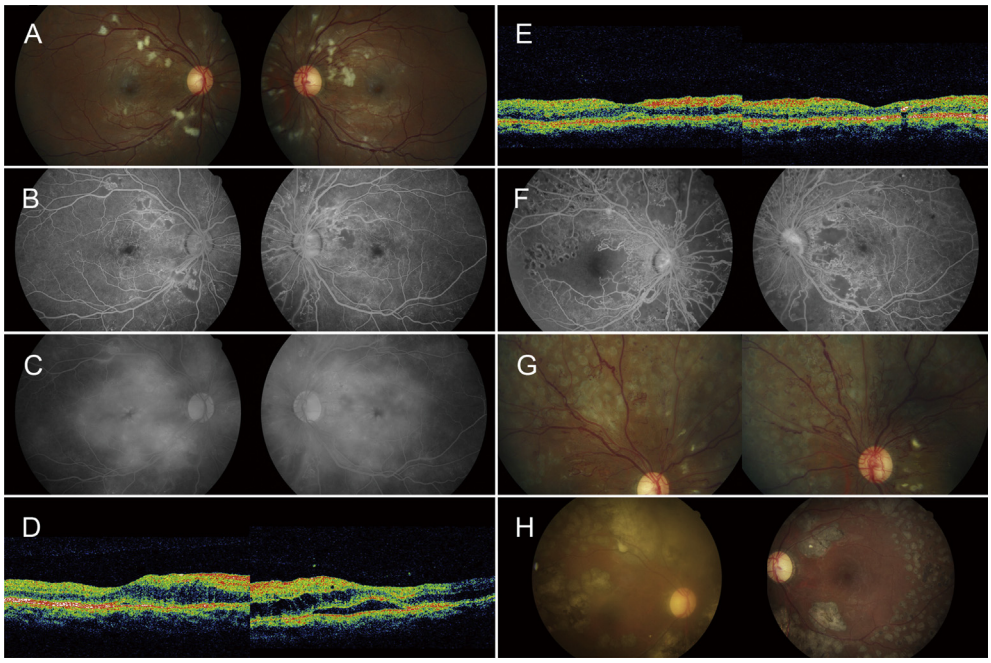

Fig. 3. Diabetic retinopathy changes in Case 5 after pancreas transplantation (PT). (A) Three weeks after PT, fundus examination showed bilateral multiple peripapillary soft exudate and marked macular edema. (B, C) Fluorescein angiography (FAG) showed a multiple peripapillary nonperfusion area in early phase and profound diffuse vascular leakage in late phase. (D) Optical coherence tomography revealed marked cystoid macular edema in both eyes. (E) Macular edema resolved significantly after intravitreal bevacizumab injection. (F) Three months later, the patient's right eye experienced macular branch retinal artery occlusion. FAG also revealed a large area of peripapillary vascular nonperfusion with intraretinal microangiopathy and venous beading. Panretinal photocoagulation (PRP) was performed for both eyes. (G) Persistent progression of diabetic retinopathy with new vessels of the optic disc and elsewhere despite extensive PRP. (H) After three intravitreal bevacizumab and triamcinolone injections and supplementary PRP, the retinopathy was finally stabilized.

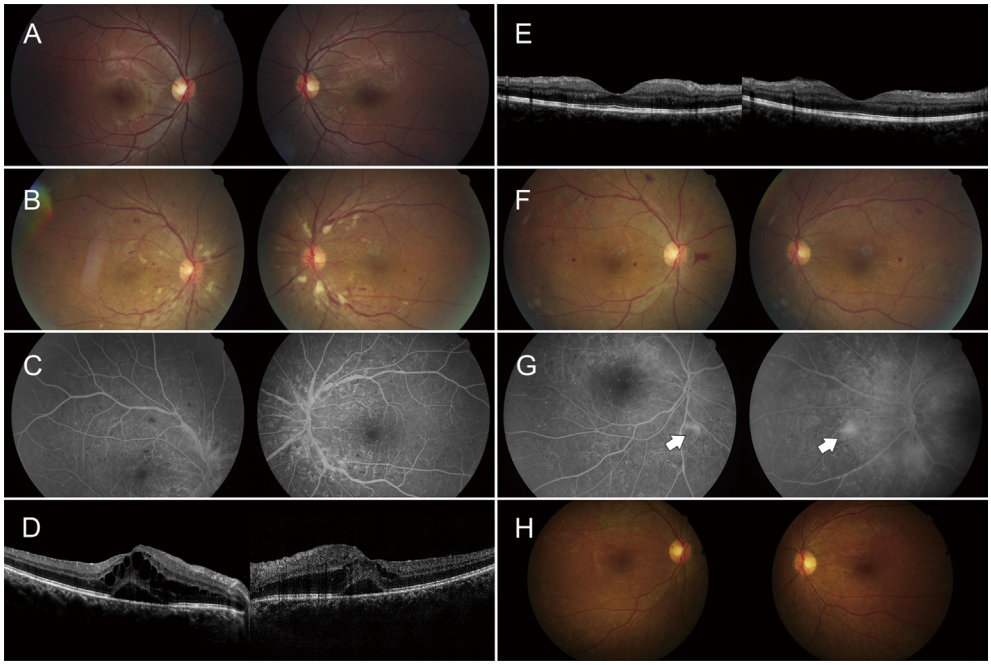

Fig. 4. Progression of diabetic retinopathy (DR) in Case 6. (A) Fundus examination before pancreas transplantation (PT) showed no DR in either eye. (B) Ten weeks after PT, fundus examination showed macular edema, peripapillary soft exudate, and splinter hemorrhage in both eyes. (C) Fluorescein angiography (FAG) showed venous beading, intraretinal microangiopathy, and numerous microaneurysms at the posterior poles. (D) Optical coherence tomography demonstrated bilateral cystoid macular edema and subretinal fluid accumulation. (E) Intravitreal bevacizumab injection was performed for both eyes, and macular edema resolved satisfactorily. (F) Nine months later, DR had progressed despite total resolution of macular edema. (G) FAG showed retinal neovascularization (arrow), and supplementary panretinal photocoagulation was performed. (H) The retinopathy regressed and remained stable at 16 months' follow-up.

IVBs and intravitreal triamcinolone injections were administered bilaterally in addition to supplementary PRP. Two years after PTA, the diabetic retinopathy had stabilized and cataract surgery was performed in the left eye. At 35 months post-PTA, the patient's BCVA was counting fingers at 20 cm in the right eye and 6/7.5 in the left eye. Fundoscopy revealed silent retina with disc pallor in both eyes (Fig. 3H). The fundus condition remained stable at 5 years post-PTA.

3.1.3. Case 6

A 23-year-old female diagnosed with type 1 DM at 14 years of age underwent PTA owing to poor DM control and the development of autonomous neuropathy and proteinuria. Mild elevation of pancreatic enzyme levels was noted in the early postoperative period, but these improved spontaneously. HbA1c was 13.0% preoperatively, and decreased to 7.4% at 2 months and 6% at 6 months after surgery.

BCVA before PTA was 6/6 in both eyes, and fundoscopy showed no diabetic retinopathy (Fig. 4A). Subjective visual blurring in both eyes with photophobia was noted 10 weeks after transplantation, and BCVA dropped to 6/10 in the right eye and 6/20 in the left eye. The anterior segment was normal except for mild posterior subcapsular lens opacity in both eyes. Dilated fundus examination revealed multiple peripapillary soft exudates and diffuse macular edema in both eyes (Fig. 4B). FAG showed venous beading and numerous microaneurysms at the posterior pole with late dye leakage but without significant peripheral microangiopathy (Fig. 4C). OCT revealed marked cystoid macular edema and subretinal fluid in both eyes (Fig. 4D). IVB was administered immediately to both eyes.

Three weeks later, BCVA had improved to 6/8.6 in the right eye and 6/10 in the left eye. The peripapillary soft exudates had decreased and the cystoid macular edema had improved significantly (Fig. 4E). PRP was performed in both eyes to prevent diabetic retinopathy progression. Six months later, NVE developed in both eyes despite the regression of macular edema (Figs. 4F and 4G). Supplementary PRP was performed subsequently in both eyes. Fundus condition became stable at 16 months after transplantation (Fig. 4H), and the final BCVA was 6/6.7 in the right eye and 6/6 in the left eye.

4. Discussion

The patients in this series either did not have diabetic retinopathy or had only mild NPDR prior to pancreas transplantation, and developed acute macular edema and peripapillary soft exudate within a few weeks after transplantation despite physiological euglycemia. Macular edema and soft exudate resolved within a few months, followed by peripheral microangiopathy, which progressed to PDR that required PRP. All patients had high HbA1c prior to transplantation, which decreased rapidly to normal levels within 2 months. After treatment, diabetic retinopathy became stable in all cases.

Bilateral acute macular edema with peripapillary soft exudate after pancreas transplantation in our cases was most likely related to the rapid fall in blood sugar levels after PTA. The patients did not have any other associated risk factors for acute macular edema and soft exudate, such as elevated blood pressure or acute pancreatitis. All of our patients had poor blood sugar control with high HbA1c prior to transplantation and a rapid, large HbA1c reduction within 2 months after transplantation. The Oslo study, which studied retinopathy changes during 1 year of tight blood sugar control in type 1 DM patients without proliferative retinopathy, found that a large and rapid fall in blood sugar level induced the development of macular soft exudate in 50% of patients after 3–6 months of intensive treatment.[13] The Diabetes Control and Complications Trial (DCCT), which compared intensive versus conventional insulin treatment in type 1 DM patients with no to moderate NPDR, also showed that the occurrence of early worsening, including the development of soft exudate and/or IRMA, was almost three times greater in the intensive treatment group than in the conventional treatment group during the 6-month follow-up period.[14] These studies showed that high baseline HbA1c and a large magnitude of HbA1c reduction are associated with early worsening of diabetic retinopathy in type 1 DM patients after intensive insulin treatment.[13,14] Some investigators postulate that the acute worsening of diabetic retinopathy after strict insulin control may be related to hypoglycemia,[13] which is an inevitable complication of intensive insulin treatment. The Oslo study reported that the frequency of hypoglycemia was higher in patients who developed macular cotton wool spots after receiving intensive insulin treatment.[13] However, analysis of the DCCT database found that severe hypoglycemia increased the risk of retinopathy in the conventional treatment group, but not in the intensive group,[15] despite a three-fold higher rate of hypoglycemia in the intensive group.[16] Our case series shows that acute worsening of retinopathy can develop even under physiological euglycemia after pancreas transplantation without any hypoglycemic episodes. This suggests that hypoglycemia may not play a critical role in the acute worsening of diabetic retinopathy after strict insulin control.

The pathogenesis of acute deterioration of retinopathy after rapid improvement in glycemic levels is unclear. However, it has been well established in both animal studies and human observation that hyperglycemia can induce increased retinal blood flow.[17–21] Studies on retinal blood flow in patients with poorly controlled DM with mild or no diabetic retinopathy showed a significant increase in retinal blood flow compared to healthy individuals.[21,22] This retinal blood flow decreased significantly after intensive insulin treatment.[17] It has been postulated that reduction in retinal blood flow accompanied by a concurrent reduction in blood glucose, which is an important metabolic substrate, could be related to the development of retinal ischemia in patients with rapid normalization of high blood sugar levels.[17]

The treatment results in our cases were good despite rapid progression to PDR after pancreas transplantation. All eyes had stable diabetic retinopathy with good final vision, except one eye that experienced macular branch retinal artery occlusion. A previous study reported that 12% of patients developed macular edema after PTA and all were resolved at the final follow-up.[10] Chow et al[12] reported that 2% of patients experienced macular edema after SPK and all resolved either

with treatment or spontaneously. These studies indicate that physiological euglycemia after pancreas transplantation cannot halt the occurrence of retinopathy; however, it can have a beneficial effect on the treatment results.

As a retrospective case series, the major drawback of this study is the lack of pretransplant documentation of retinopathy by fundus photography in some patients. Retinopathy status was documented by ophthalmologists through illustration and description; however, none of them mentioned noticing macular soft exudate or edema during examination, and all patients had 6/6 BCVA before transplantation.

In conclusion, this is the first case series of acute macular edema with peripapillary soft exudate after PTA. All patients had high pretransplant HbA1c with mild or no diabetic retinopathy, and progressed to severe NPDR or PDR despite physiological euglycemia. All cases developed stable diabetic retinopathy after PRP without further progression during the follow-up period. We hypothesize that high pretransplant HbA1c and the rapid and large magnitude of blood sugar normalization were most likely related to the disease course. We are now carrying out a retrospective study to investigate risk factors for acute macular edema and peripapillary soft exudate following pancreas transplantation. Further studies are warranted to investigate retinopathy changes and identify risk factors for diabetic retinopathy progression after pancreas transplantation.

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