

# Newly diagnosed diabetes mellitus patients presenting with proliferative diabetic retinopathy as an initial sign

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## Abstract

• **AIM:** To investigate the clinical features of newly diagnosed diabetes mellitus (NDM) patients showing proliferative diabetic retinopathy (PDR) as an initial sign.

• **METHODS:** As a retrospective case series, the medical records of a total of four hundred and thirty-two patients who underwent a vitrectomy due to PDR were reviewed to find the subjects. Of 432 patients, six cases of NDM patients showing PDR as an initial sign were included and analyzed with their systemic and ocular features. Main outcome measures: the systemic features and ocular features [preoperative and postoperative best corrected visual acuity (BCVA), intraoperative findings].

• **RESULTS:** The mean onset age of visual symptoms was 36.3 years old. The mean serum insulin and C-peptide titer was below the normal range. The mean fasting plasma glucose was 178mg/dL and the mean postprandial 2h plasma glucose was 306mg/dL. The mean HbA1c at diagnosis was 11.02%. In all cases, an acute progressive fibrovascular proliferation was observed. Intraoperative retinal tears were found in three cases of six. The mean preoperative BCVA was  $+0.67 \pm 0.58$  logMAR and the mean BCVA at postoperative 6 months was  $+0.20 \pm 0.30$  logMAR.

• **CONCLUSION:** All patients were considered to have latent autoimmune diabetes in adults (LADA). A rapid deterioration of kidney function as well as poor diabetic control status at diagnosis was observed in all six cases. The ocular features of the patients showed acute progressive fibrovascular proliferation and relatively favorable postoperative visual acuity.

• **KEYWORDS:** fibrovascular proliferation; latent autoimmune diabetes in adults; diabetes mellitus; proliferative diabetic retinopathy

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## INTRODUCTION

Diabetes mellitus (DM) patients usually present with diabetic symptoms such as polydipsia, polyuria, weight loss and general weakness. In an ophthalmologic view, diabetic retinopathy is a major cause of blindness and its severity is known to be correlated with the duration of diabetes and the degree of plasma glucose control.

The prevalence of diabetic retinopathy in patients with newly diagnosed type 2 DM is known to vary between 10% and 20% in population-based studies<sup>[1,2]</sup>. Otherwise, the prevalence of diabetic retinopathy in type 1 DM was found to be almost 100% over a 20 year period but rarely develops within initial 5 years in previous study<sup>[3]</sup>.

The predisposing factors of diabetic retinopathy include the duration of diabetes, glycemic control and blood pressure<sup>[4]</sup>. Other possible factors of diabetic retinopathy such as the onset age, serum lipids, and body mass index is still unclear<sup>[5]</sup>. Endocrinologists refer a significant number of diabetic patients due to complaints of a decreased visual acuity or floater and some of them are diagnosed with diabetic retinopathy. Severe retinopathy shortly after the diagnosis of type 1 DM is very rare but described in previous reports<sup>[6,7]</sup>. One case in which PDR was observed in a funduscopy examination at an initial ophthalmic visit immediately after the diagnosis of DM has been already reported<sup>[8]</sup>. However, the cases showing PDR at an initial ophthalmic visit before the diagnosis of DM have never been reported. The authors have had patients who visited our department of ophthalmology with a visual disturbance and had findings suspicious of PDR. These patients would be referred to the endocrinologist who would diagnose them with newly diagnosed diabetes mellitus (NDM). To investigate the systemic and ocular features of these patients, we performed this study.

## SUBJECTS AND METHODS

To identify the subjects for this study, we retrospectively reviewed the medical records of 432 patients who had undergone a vitrectomy due to PDR from March 2002 to December 2011 in our department of ophthalmology. Among them, six cases of NDM patients showing PDR as an initial

## Diabetes mellitus diagnosed with proliferative retinopathy

**Table 1** Baseline characteristics and diabetic status of case patients

Case	Onset age of NDM	Gender	Family history of diabetes mellitus	Fasting plasma glucose (70-110mg/dL)	Serum insulin Titer (2.0-25.0IU/dL)	Serum C-peptide (0.5-4.0ng/mL)	HbA1c (2.7%-5.8%)
1	39	F	Yes	251	< 2.0	0.3	12.5
2	42	M	Yes	135	2.97	0.1	10.4
3	34	F	Yes	146	< 2.0	0.4	9.1
4	30	M	Yes	178	< 2.0	0.8	11.0
5	42	M	Yes	221	< 2.0	0.2	11.2
6	31	F	Yes	137	< 2.0	0.4	11.9
Mean	36.3			178		0.37	11.02

( ): Reference value, unit; M: Male; F: Female; HbA1c: Glycosylated hemoglobin.

**Table 2** The lipid profile, body mass index (BMI) and renal function test results of the patients

Case	Total cholesterol (0-250mg/dL)	LDL cholesterol (70-150mg/dL)	TG (0-160mg/dL)	BMI <sub>2</sub> (kg/m <sup>2</sup> )	Proteinuria of initial visit	Proteinuria after 6 months	Creatinine of initial visit (0.6-1.2mg/dL) <sup>+</sup>	Creatinine after 6 months (0.6-1.2mg/dL)	GFR of initial visit (mL/min/1.73m <sup>2</sup> )	GFR after 6 months (mL/min/1.73m <sup>2</sup> )
1	335	207	255	25.14	3+	3+	0.7	1.4	99.7	48.2
2	125	69	87	21.7	2+	4+	2.1	2.2	67.4	30.3
3	187	134	94	22.7	-	Unknown	0.8	1.0	78.9	Unknown
4	196	119	51	18.3	2+	3+	1.0	1.7	89.1	49.4
5	178	128	136	24.2	-	-	0.8	1.0	77.2	68.1
6	154	82	169	28.2	2+	2+	0.7	1.0	103.9	89.1
Mean	195.8	123.2	132	23.4			1.02	1.38	86.03	57.02

( ): Reference value, unit; LDL: Low density lipidprotein; TG: Triglyceride; BMI: Body mass index; GFR: Glomerular filtration rate.

**Table 3** The duration of visual disturbances, preoperative and BCVA and intraoperative findings of the patients

Case	Duration of visual disturbance (weeks)	Initial BCVA (Snellen)	Preop. BCVA		Postop. months BCVA		NVI	Intraoperative findings	
			logMAR	Snellen	logMAR	Snellen			
1	R	1	CF 50cm	+2.0	CF 50cm	+0.10	20/25	No	VH, fibrovascular membrane proliferation
	L	1	20/40	+0.30	20/40	+0.50	20/63	No	VH, fibrovascular membrane proliferation, retinal tear
2	R	4	CF 100cm	+1.70	CF 100cm	LP (+)	LP (+)	No	VH, TRD, retinal tear
	L	4	20/20	0.00	20/20	0.00	20/20	No	Not operated
3	R	2	20/25	+1.10	20/250	+0.10	20/25	No	VH, fibrovascular membrane proliferation
	L	2	20/25	+1.40	20/500	0.00	20/20	No	VH, fibrovascular membrane proliferation, retinal tear
4	R	1	20/200	+1.0	20/200	+0.10	20/25	No	VH, fibrovascular membrane proliferation
	L	1	20/250	+1.10	20/250	0.00	20/20	No	VH, fibrovascular membrane proliferation
5	R	4	20/25	+1.22	20/320	+0.20	20/32	No	VH, fibrovascular membrane proliferation
	L	4	20/32	+1.40	20/500	0.00	20/20	No	VH
6	R	4	20/100	+0.70	20/100	+0.30	20/40	No	VH
	L	4	20/100	+0.70	20/100	+1.00	20/200	No	VH, fibrovascular membrane proliferation, TRD

NVI: Neovascularization of iris; R: Right eye; L: Left eye; CF: Counting fingers; LP: Light perception; VH: Vitreous hemorrhage; TRD: Tractional retinal detachment.

sign were included and analyzed with systemic and ocular features. All six patients' baseline characteristics, laboratory data, preoperative and postoperative BCVA, intraoperative findings and treatment modalities were identified. The diagnosis and the surgery were done by a single experienced surgeon.

## RESULTS

The mean onset age of visual disturbance was 36.3 years (range: 30-42 years) and a family history of DM was identified in all patients. The serum insulin titer was below the minimal detectable concentration of 2.0IU/dL in five of six patients. The serum C-peptide titer was measured below the normal range (0.5-4.0ng/mL) in five of six patients and the mean value of the serum C-peptide titer of all patients

was 0.37ng/mL, which was also below the normal range. The mean fasting plasma glucose was 178mg/dL, which was above the normal range of 64.8-104.4mg/dL. The mean HbA1c level at the time of diagnosis was 11.02%, which was above the normal range (2.7%-5.8%) (Table 1). Proteinuria was present in four of six patients at initial visit. Considering the changes in serum creatinine and GFR values, the kidney function was deteriorated in all the patients within 6 months (Table 2). The mean preoperative BCVA was +0.67±0.58 logMAR and the mean BCVA at postoperative 6 months was +0.20±0.30logMAR. On intraoperative retinal findings, an acute progressive fibrovascular proliferation was observed in all cases and retinal tears were found in three of six cases (Table 3).

**Case 1** A 39 year-old female patient was referred to our hospital by an ophthalmic private physician. She complained of an acute visual disturbance of the right eye which had occurred 1 week before. Her initial BCVA and intraocular pressure (IOP) were counting fingers at 50cm distance and 19mmHg in the right eye, 20/40 and 18mmHg in the left eye. She did not have any comorbidities and appeared generally well for her physical condition. The patient had no history of alcohol consumption, smoking, hypertension. There was a known family history of DM. A funduscopy examination was performed immediately after her visit and the funduscopy showed vitreous hemorrhage and subhyaloid hemorrhage in the right eye, extensive neovascularization of the disc (NVD) and hard exudates (HE) in the left eye. PDR was suspected. A panretinal photocoagulation (PRP) and intravitreal bevacizumab (Avastin<sup>®</sup>, 1.25mg/0.05mL) injection was performed on the first day of the initial visit and the patient was referred to the department of endocrinology which resulted in confirming the NDM. A pars plana vitrectomy was performed in the right eye. Also diffuse fibrovascular membrane proliferation adjacent to the optic disc and retinal vessels and diffuse retinal hemorrhage were found during the operation. A fibrovascular membrane segmentation and endolaser photocoagulation were performed and followed by intravitreal Avastin injection as the final procedure.

Six months after surgery of the right eye, vitreous hemorrhage had occurred in the left eye and a vitrectomy was done for the left eye. A retinal tear was found around the 1 o'clock fibrovascular membrane. A barrier laser photocoagulation and endolaser photocoagulation along with fluid-gas exchange (14% C<sub>3</sub>F<sub>8</sub> gas) were performed.

Six months after the surgery of left eye, her BCVA had recovered to 20/25 in the right eye and 20/63 in the left eye. In the postoperative optical coherence tomography (Stratus OCT, Carl Zeiss Meditec, Germany) image, diabetic macular edema (DME) of both eyes was identified.

**Case 2** A 42 year-old male patient visited our department of ophthalmology. He complained of visual disturbance in the right eye that began 1 month before. His BCVA and IOP on visit were counting fingers at 100cm distance and 21mmHg in the right eye, 20/20 and 19mmHg in the left. He had been diagnosed with hypertension 5 years prior to visiting us. The patient had a smoking history of 30 pack-years and a family history of DM. The patient did not have any history of alcohol consumption. On funduscopy examination, severe bleeding in the vitreous cavity of the right eye prevented a thorough evaluation of the fundus. Neovascularization was found in the left eye around the equator and the optic disc.

An eyeball ultrasound biomicroscopy (B-scan, Hi-Scan, OPTIKON. 2000, Rome, Italy) was performed and a focal lesion suggesting tractional retinal detachment (TRD) in the right eye was found. An immediate vitrectomy of the right eye was planned, and the patient was referred to the department of endocrinology where NDM was confirmed. However, the patient delayed treatment and his visual acuity continued to deteriorate due to PDR, resulting in a loss of 2 months of follow up. After the 2 months follow-up loss, the patient underwent a vitrectomy. During the operation, tractional membrane segmentation was performed.

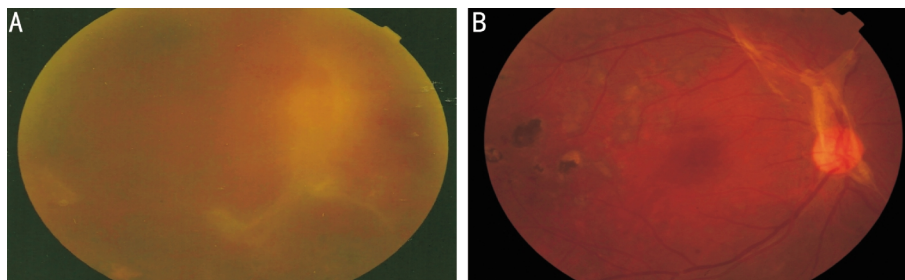
A retinal tear was found around the 10 o'clock fibrovascular membrane. Barrier laser photocoagulation and endolaser photocoagulation along with fluid-gas exchange (14%, C<sub>3</sub>F<sub>8</sub> gas) were performed.

One month after surgery of the right eye, a rhegmatogenous retinal detachment and proliferative vitreoretinopathy were seen on funduscopy examination, resulting in an additional surgery of cryopexy and silicone oil injection.

Currently, the vitreous cavity of the right eye shows a total retinal detachment (RD) and proliferative vitreoretinopathy, which resulted in the final BCVA of only light perception. The patient had a PRP with intravitreal Avastin injection to the left eye and has been followed in the outpatient department. His BCVA of the left eye was 20/20.

**Case 3** A 34 year-old female patient visited our department of ophthalmology. She complained of floaters in both eyes which began 2 weeks prior. Her initial BCVA and IOP on visit were 20/25 and 18mmHg in the right eye, 20/25 and 14mmHg in the left eye. She had never been diagnosed with any other diseases and had no history of smoking or alcohol consumption. She had a family history of DM.

Multiple retinal hemorrhage and neovascularization of elsewhere (NVE) was found in the retina, requiring an immediate PRP. NDM was suspected. During the follow-up, a bilateral thick vitreous hemorrhage occurred, hindering observation of the retinal surface. Consequently, a B-scan was performed to estimate the retinal status; showing vitreous hemorrhage in company with the tractional membrane. Her preoperative BCVA and IOP of the right eye were 20/250 and 25mmHg. A vitrectomy was performed on the right eye. Also fibrovascular membrane segmentation and endolaser photocoagulation was done. Four weeks after the surgery of the right eye, her preoperative BCVA and IOP of the left eye were 20/500 and 19mmHg. A vitrectomy was performed to the left eye. A retinal tear was found around the 2 o'clock fibrovascular membrane. A barrier laser and endolaser photocoagulation along with a fluid-gas exchange were performed.



**Figure 1 Fundus photograph of the right eye in a 30 year-old male** A: A preoperative fundus photograph. The vitreous hemorrhage is so severe that the fundus is not clearly visible. Also optic nerve head and fibrovascular membrane proliferation is dimly seen; B: A Fundus photography of the right eye 6 months after the operation. The PRP scar is seen and the tractional remnant is placed on the superotemporal, superonasal side and upper pole of optic nerve head.

Six months after the surgery, the patient had a BCVA of 20/25 in the right eye and 20/20 in the left, respectively. Except for the epi-center lesion, no other complications occurred.

**Case 4** A 30 year-old male patient visited our department of ophthalmology. He complained of decreased visual acuity in both eyes with distance that began 1 week before. He was referred by a private eye clinic. His initial BCVA and IOP on visit were 20/200 and 16mmHg in the right eye, 20/250 and 17mmHg in the left. He had never been diagnosed with any other diseases but had a history of smoking and alcohol consumption for over 10 years. He had a family history of DM. At the initial examination, the right fundus was not fully visible due to vitreous hemorrhage. Diffuse fibrovascular proliferation was shown near the posterior pole of the right eye (Figure 1A). A B-scan was performed in the right eye and thick vitreous hemorrhage along with a tractional membrane was observed. After a week, a vitrectomy was done. Fibrovascular membrane segmentation and endolaser photocoagulation were performed in the right eye (Figure 1B). Six months after surgical treatment for the right eye, a left eye vitrectomy was performed. No other findings except for the fibrovascular membrane proliferation were observed in the left eye.

Six months after the surgery, the patient's BCVA was 20/25 in the right eye and 20/20 in the left. During the postoperative follow up, NVE in both eyes and DME in the right eye were confirmed by fluorescein angiography (FAG) and OCT.

**Case 5** A 42 year-old male patient visited our department of ophthalmology. He complained of blurred vision in both eyes that began one month before. He was referred by a private eye clinic. His initial BCVA and IOP were 20/25 and 15mmHg in the right eye, 20/32 and 17mmHg in the left eye. He had never been diagnosed with any other diseases but had a 20 year history of smoking. The patient had a family history of diabetes. The patient did not have any history of alcohol consumption.

The fundus examination showed NVE with soft exudates. PDR was suspected. The patient underwent a PRP and intravitreal Avastin injections. During the follow-up, diffuse vitreous hemorrhage and fibrovascular membrane proliferation in the right eye were found on funduscopy examination. His preoperative BCVA and IOP were 20/320 and 15mmHg on the right eye. A vitrectomy was performed of the right eye.

Four months after surgery of the right eye, vitreous hemorrhage occurred in the left eye. His preoperative BCVA and IOP of left eye were 20/500 and 17mmHg. A vitrectomy was also performed in the left eye. The epi-center lesion was seen as a postoperative finding. His BCVA 6 months after the left eye surgery had recovered to 20/32 in the right eye, and 20/20 in the left.

**Case 6** A 31 year-old female patient visited our department of ophthalmology. She complained marked blurred vision in both eyes which had been present for a month. Her BCVA and IOP at the visit were 20/100 and 13mmHg in the right eye, 20/100 and 15mmHg in the left eye, respectively. She complained that the symptoms affected her activities of daily living.

She did not have any medical history, operation history or other symptoms that lead us to suspect diabetes. She had no history of smoking or alcohol consumption but had a family history of DM.

During the funduscopy examination of the right eye, vitreous hemorrhage and retinal hemorrhage were observed in the vitreous cavity. The fundus of the left eye was invisible owing to the massive vitreous hemorrhage. We detected TRD by B-scan on the left eye and a prompt vitrectomy was done. On the right eye, we performed a PRP and intravitreal Avastin injection. After that, a vitrectomy was done on the right eye.

The BCVA at the postoperative 6 month follow-up was 20/40 in the right eye and 20/200 in the left. A DME and NVE were confirmed in both eyes by OCT and FAG.

## DISCUSSION

Several systemic and ocular features of NDM patients that showed PDR as the initial sign were uncovered. They are listed below.

First, considering the systemic features, the average onset age of visual disturbance was 36.3 years (30-42) and proteinuria was confirmed in 4 patients of the total 6 patients at the time of onset of visual disturbance. The initial visual acuity was worse in the patients with proteinuria (Table 3).

The relationship between DM retinopathy and DM nephropathy has been described frequently in previous studies. There have been reports that microalbuminuria suggesting early stage DM nephropathy is closely related with the occurrence and severity of PDR<sup>[9]</sup>. In DM nephropathy patients, other microvascular complications such as DM retinopathy and DM neuropathy accompany the majority of cases<sup>[3,10]</sup>. Conversely, there has been a report that microalbuminuria always appears in a case of advanced DM retinopathy. In that case, a histologic change in the glomeruli of kidney has already existed as a microvascular change<sup>[11]</sup>.

Consequently, even a case of simply showing microalbuminuria without a decline in the glomerular filtration rate (GFR) or a rise in the serum creatinine level can progress to DM retinopathy. According to a prior study from the American Diabetes Association, 35% of symptomatic DM retinopathy patients showed overt proteinuria, an increase in serum BUN, and creatinine levels<sup>[12]</sup>. In our study, all the patients showed the decrease in the GFR and increase in the serum creatinine level after a six month follow-up. All six cases of patients can be considered to accompany DM nephropathy and to have a rapid deterioration of renal function. Especially in case 1, 2 and 4, a marked decline in GFR was observed after the six month follow-up. Conclusively, a more thorough monitoring of DM nephropathy is necessary for NDM patients with PDR.

Another systemic feature of our cases is that almost all the patients (five of six patients) had a serum insulin and C-peptide titer below the normal range, considering them to be classified as insulin-dependent DM (IDDM). A high serum HbA1c level (mean 11.02%) along with high fasting plasma glucose (mean 178mg/dL) and postprandial 2h plasma glucose (mean 306mg/dL) allow us to estimate that all the patients were in a status of poor glycemic control. All patients were diagnosed with NDM from the department of endocrinology and were prescribed lifestyle modification, oral diabetes medication or insulin therapy. Generally, IDDM patients present with typical systemic diabetic symptoms such as: polyuria, thirst, weight loss and are younger than their twenties at the age of onset. Additionally,  $\beta$ -cell destruction

by the autoantibody to the pancreatic islet cell, resulting in absolute insulin dependencies can be thought of as its clinical feature. The patients of this study showed a titer of serum insulin and C-peptide below the normal range. Patients had an average onset of their thirties, compared to the known average onset of tenths in IDDM. Also, the patients had never complained of any conventional systemic diabetic symptoms before the initial ophthalmic visit. This type of IDDM with a slow-onset is called LADA (Latent autoimmune diabetes of adults), or type 1.5 DM as a subtype of IDDM<sup>[13]</sup>.

There have been several reports that other factors such as obesity or increased BMI may be related to the occurrence and severity of DM retinopathy<sup>[2,14]</sup>. However, none of our cases were included in the obesity based criteria on the BMI values.

Other systemic features of patients in this study were that all the patients had a family history of DM and had experienced a previous severe stress such as bankruptcy, divorce and family problems.

Next, the ocular features of our cases were that an acute progressive fibrovascular membrane proliferation was found in both eyes and that a postoperative visual outcome was relatively favorable when considering the poor preoperative retinal status

The Case 2 in this study had PDR along with TRD at initial visit and was in need of prompt surgical intervention. However, the patient delayed treatment and the visual acuity had deteriorated by PDR, so resulting in a 2 month delay of surgery. In contrast to the other five patients who showed a favorable outcome of visual acuity after the surgery, this patient already had an advanced stage of TRD while planning the vitrectomy. In addition, a retinal tear which was not discovered before the operation due to vitreous hemorrhage was found during the operation. So we performed a barrier laser photocoagulation, fluid-gas exchange and silicone oil injection, but the patient had lost sight in the right eye (only light perception remained) resulting from a postoperative total RRD and PVR.

In three cases of six, a retinal tear adjacent to the tractional membrane was identified. We estimate that the retinal tear may have developed by tractional force of the fibrovascular membrane. The other two cases that had a retinal tear showed a favorable postoperative BCVA. We compared preoperative BCVA with the BCVA 6 months after the surgery of each patient. A Wilcoxon signed rank test was used to statistically analyze the difference in BCVA. A postoperative BCVA was relatively more favorable than the preoperative BCVA but not significant statistically ( $P=0.2$ ).

As shown in this study, the NDM patients showing PDR

needed a prompt and proper intervention in that a poor visual outcome can be caused by the missing appropriate timing of treatment and by the occurrence of a TRD and retinal tear.

These patients did not have any diabetic symptoms before the initial ophthalmic visit. Also, a proper DM screening test was difficult to perform, which prevented the timely diagnosis and treatment of DM. When we had first treated the patient with severe retinopathy in both eyes without a known underlying systemic disease, a clinician should always consider the possibility of PDR caused by NDM. As the microvascular complications including retinopathy tend to develop very rapidly in these groups of patients, thorough and instant ophthalmologic management as well as cooperation with the endocrinologists and nephrologists is needed. Additionally, frequent follow-up and adequate education for patients is required in order to increase not only an understanding of their own diseases but also compliance to the treatment. Further study of these cases is required in the future.

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