

Case Report

Advanced Exudative Retinopathy with Neovascular Glaucoma as the Clinical Presentation of Diabetes Mellitus and Severe Combined Hyperlipidemia: A Case Report

Suthasinee Sinawat MD*,
Sukhumal Thanapaisai MD*, Supat Sinawat MD**

* KKU Eye Center, Department of Ophthalmology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

** Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

A 50-year-old man presented with bilateral progressive visual loss for 5 months. Visual acuity was reduced to counting fingers in the right eye and light perception in the left. Although neovascularizations were detected in the angles of the eyes, neovascular glaucoma and rubeosis iridis were demonstrated only in the left. Fundus examination showed bilateral advanced exudative retinopathy in both eyes. Severe attenuated retinal arteries and enlarged cupping with disc pallor were observed in the left eye. Generalized eruptive xanthomas were found on the back and extremities. Extreme dyslipidemia (serum cholesterol 1,311 mg/dl and triglycerides 6,356 mg/dl) and diabetes mellitus (fasting plasma glucose 325 mg/dl and HbA1c 12.1%) were first diagnosed. The serum lipid profiles and glucose levels were dramatically decreased within a month after treatment with subcutaneous insulin injections and oral hypolipidemic agents; notwithstanding, his vision was not significantly improved, even after treatment with intravitreal anti-VEGF injection, intravitreal steroid injection and panretinal photocoagulation.

Conclusion: The principle causes of advanced exudative retinopathy are severe breakdown of the blood-retinal barrier due to diabetes mellitus and altered retinal pigment epithelium lipid metabolism. In our patient, central retinal vascular occlusion was also the suspected cause of neovascular glaucoma.

Keywords: Exudative retinopathy, Dyslipidemia, Neovascular glaucoma, Diabetes mellitus

J Med Assoc Thai 2014; 97 (Suppl. 10): S110-S114

Full text. e-Journal: <http://www.jmatonline.com>

Type 2 diabetes mellitus (DM) is commonly associated with dyslipidemia. Although diabetic nephropathy is associated worldwide with a higher level of plasma triglyceride and a lower level of HDL-cholesterol, among patients with good control of LDL-cholesterol, retinopathy is less associated with these lipids. The respective association of triglycerides and HDL-cholesterol with retinopathy may be dependent on other confounding factors for microvascular disease, particularly hypertension and hemoglobin A1c⁽¹⁾.

We herein report a 50-year-old man with type 2 DM and severe combined hyperlipidemia who presented with advanced exudative retinopathy and neovascular glaucoma, resulting in blindness.

Correspondence to:

Thanapaisai S, KKU Eye Center, Department of Ophthalmology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

Phone: 043-363-010, Fax: 043-348-383

E-mail: sukhumal54303@gmail.com

Case Report

A 50-year-old man suffered from ocular pain in the left eye for one month and bilateral progressive visual loss for 5 months. The patient also noticed non-itching skin papules and nodules on his trunk and extremities 2 months prior to presentation. No abdominal pain or jaundice was mentioned. He was an alcoholic and a heavy smoker. The patient denied having any underlying disease(s) or prior treatments. Family history was uninformative since he lived alone.

Physical examinations on admission revealed a suitable body mass index (21.48 kg/m²) and elevated blood pressure (145/85 mmHg). Generalized yellowish papules were scattered on the trunk, hands, and extensor areas of the elbows, knees and ankles (Fig. 1). His visual acuity (VA) was reduced to counting fingers at 1 foot (CF 1') in the right eye and light perception (LP) in the left. Intraocular pressure (IOP) was 14 and 30 mmHg, respectively. Although neovascularizations were detected in the angles of the eyes, neovascular

glaucoma and rubeosis iridis were demonstrated in only the left. Reversed relative afferent pupillary defect was detected in the right eye.

Fundoscopy revealed marked subretinal hard exudates throughout the fundus in both eyes; however, the amount was greater in the right eye while retinal vessels were more narrowed in the left. Retinal neovascularizations were clearly identified in the right eye. Enlarged cupping with disc pallor was detected in the left eye. The extent of the confluent retinal exudates and hemorrhages seemed to be more severe than would be expected in typical diabetic retinopathy (Fig. 2). Due to renal insufficiency, fluorescein angiography could not be done in this patient.

The biochemical evaluations and systemic investigations are outlined in Table 1. The most significant abnormalities were severe combined hyperlipidemia, extreme serum cholesterol (1,311 mg/dl) and triglycerides (6,356 mg/dl). Lipemic serum was detected during venopuncture; such that the separation between lipid and serum was more obvious with time (Fig. 3). Type 2 DM was first diagnosed by

fasting plasma glucose (325 mg/dl). His kidney function was poor and he had elevated serum creatinine (2.4 mg/dl). Acute pancreatitis and hypothyroidism were, however, not detected. Although marked proteinuria was found, the value did not reach the criteria for diagnosing nephrotic syndrome. Our differential diagnosis was progressive outer retinal necrosis, which is commonly found in HIV-positive patients. The anti-HIV antibody tests for this patient were, however,

Table 1. Biochemical evaluation and investigation

	Patient value	Normal value
Lipid profile		
Total cholesterol	1,311 mg/dl	100-240 mg/dl
LDL-c	97 mg/dl	<110 mg/dl
HDL-c	26 mg/dl	40-59 mg/dl
Triglyceride	6,356 mg/dl	30-250 mg/dl
Biochemical evaluation		
BUN	27.3 mg/dl	7-20 mg/dl
Cr	2.3 mg/dl	0.7-1.4 mg/dl
Total protein	7.1 mg/dl	6.3-8.2 g/dl
Albumin	3.5 mg/dl	3.5-5.2 g/dl
Liver function test	Within normal limits	
Thyroid function test	Within normal limits	
Serum amylase	71 U/L	30-110 U/L
Anti-HIV antibody	Non-reactive	
Urine analysis		
Total protein in 24-hr urine	461 mg/ml	40-50 mg/ml
Investigation		
CXR	Normal findings	
EKG	Normal sinus rhythm	



Fig. 1 Eruptive xanthomas occurred on the hands, back, extensor area of elbows and knees.

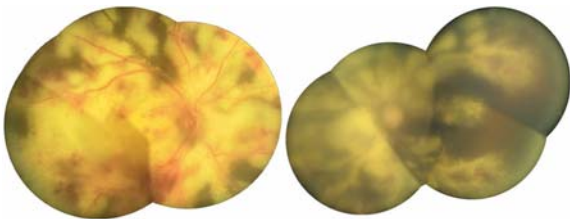


Fig. 2 Fundus examination showed extreme exudative retinopathy in both eyes. Severe attenuated retinal arteries, enlarged cupping with disc pallor were demonstrated in the left eye.



Fig. 3 Change of lipemic serum over time.

negative.

Maximal anti-glaucomatous drugs and 1% prednisolone acetate eye drops were prescribed. The patient was treated with an intravitreal injection of 1.25 mg bevacizumab in both eyes. Due to the severe exudative retinopathy, we decided to inject 4 mg of triamcinolone acetate into the vitreous cavities 1 week later. Panretinal photocoagulation was also performed in both eyes during hospitalization. We consulted an endocrine specialist, psychiatrist, nutritionist and social worker for collaboration in proper management. The systemic treatments included: oral gemfibrozil (1,200 mg/day), diltiazem (60 mg/day) and subcutaneous mixtard injection (0.5 IU/kg/day). For the skin lesions, we prescribed 0.05% clobetasol propionate, a topical corticosteroid.

A month later, his VA remained unimproved from the first presentation. CF 1' persisted in the right eye and LP in the left eye. The neovascularizations, however, had completely regressed. The right and left IOP was 18 mmHg and 33 mmHg, respectively. Although the IOP was uncontrolled in the left eye, the patient no longer suffered from ocular pain. Gonioscopy revealed a totally open angle in the right eye and a totally closed angle in the left, due to the peripheral anterior synechia. Fundus examination demonstrated the regression of hard exudates and hemorrhages in both eyes; notwithstanding, ghost vessels were seen in all quadrants of the retina in the left eye. The respective level of serum total cholesterol and triglycerides was reduced to 585 mg/dl and 1,017 mg/dl. Fasting plasma glucose was 178 mg/dl. Intravitreal-bevacizumab re-injection was done in both eyes. Due to socioeconomic constraints, the patient could not attend the follow-up, so we referred him to a nearby local hospital.

Discussion

Both hyperglycemia and hypercholesterolemia cause endothelial dysfunction and the breakdown of the blood-retinal barrier, leading to extravasation of fluid and lipoprotein. ApoB lipoproteins which present in the retinas of diabetics in proportion to the severity of retinopathy and can cause damage to the retinal capillaries. This finding supports the concept that abnormalities in intraretinal lipid transportation might be more important than high plasma lipid levels in the pathogenesis of diabetic retinopathy⁽²⁻⁴⁾.

Although diabetes mellitus plays a role in secondary causes of hyperlipidemia, diabetics rarely

have severe combined hyperlipidemia, viz., excess cholesterol and triglycerides. Most diabetics have triglyceride levels <400 mg/dl. Severe combined hyperlipidemia usually has an inherited basis such as dysbetalipoproteinemia. Expression of the genetic potential only occurs when genetically-inherited predisposing factors interact with metabolic factors that exacerbate hyperlipidemia. Type 2 DM is a prominent risk factor for the expression of combined hyperlipidemia⁽⁵⁾. Lipoproteins can deposit in dermal tissue, retinal tissue, arterial wall, kidney, spleen and bone marrow^(6,7). Affected individuals may develop eruptive xanthomas, acute pancreatitis, coronary heart disease or peripheral vascular disease. Patients with severe combined hyperlipidemia may also have ocular manifestations, especially eyelid xanthelasma and corneal arcus⁽⁸⁾. Due to the unremarkable family history of our patient and the lack of laboratory testing, the diagnosis of genetic lipoprotein disorder (i.e. familial dysbetalipoproteinemia, which can manifest as severe combined hyperlipidemia with xanthomas) could not be accomplished. Although other associated factors (i.e. nephrotic syndrome, hypothyroidism and pancreatitis) were investigated, alcohol consumption was the only factor confirmed.

Ocular manifestations of dyslipidemia include eyelid xanthelasma, palpebral xanthoma, corneal arcus, lipid keratopathy, crystalline stromal dystrophy, lipemic aqueous, whitening of limbal vessels, exudative retinopathy, and lipemia retinalis. Our patient, however, presented only exudative retinopathy. In this case, neovascular glaucoma, which is a consequence of retinal ischemia, may have been the result of (a) advanced proliferative diabetic retinopathy or (b) central retinal vascular occlusion. Owing to the ghost vessels observed in the left eye, central retinal vascular occlusion was suspected, which would explain the smaller amounts of retinal hard exudate and why rubeosis iridis was in only the left eye.

The primary goal of treatment in diabetic dyslipidemia is to reduce the risk of coronary heart disease by lowering the LDL-cholesterol level⁽⁹⁾. The initial management of our patient was, as a consequence, focused upon lifestyle modifications plus glycemic and lipid control. After 1 month of treatment, the respective serum lipids and glucose level were significantly decreased and followed by the regression of retinal hard exudates in both eyes. This observation is similar to previous studies in which the lowering of serum lipids and glucose was accompanied by a reduction of retinal hard exudates⁽¹⁰⁻¹³⁾. The

potential for systemic lipid modulation to prevent visual loss remains unclear. In the recent FIELD study (Fenofibrate Intervention and Event Lowering in Diabetes), fenofibrate treatment resulted in a 30% reduction in the need for laser photocoagulation in diabetic patients⁽¹⁴⁾.

Our patient had the most severe advanced exudative diabetic retinopathy that has been reported in the literature. His ocular problems led to the first diagnosis of type 2 diabetes mellitus and severe combined hyperlipidemia. All ocular treatment modalities-including intravitreal anti-VEGF injection, intravitreal steroid injection and panretinal photocoagulation-were prescribed for our patient, notwithstanding, bilateral blindness occurred.

Conclusion

The principle causes of advanced exudative retinopathy are severe breakdown of the blood-retinal barrier due to diabetes mellitus and altered retinal pigment epithelium lipid metabolism. If the blood-retinal barrier were to have remained in place, lipemia retinalis would have been found and blindness might not have occurred. Central retinal vascular occlusion was still the suspected cause of the neovascular glaucoma in our case.

Acknowledgement

The authors thank (a) the patient for his consent and participation, (b) Dr. Panwad Uthiyo for data collection, (c) the Center of Cleft Lip-Cleft Palate and Craniofacial Deformities, Khon Kaen University in association with Tawanchai Project for its support and (d) Mr. Bryan Roderick Hamman for assistance with the English-language presentation.

Potential conflicts of interest

None.

References

1. Sacks FM, Hermans MP, Fioretto P, Valensi P, Davis T, Horton E, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries. *Circulation* 2014; 129: 999-1008.
2. Wu M, Chen Y, Wilson K, Chirindel A, Ihnat MA, Yu Y, et al. Intraretinal leakage and oxidation of LDL in diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2008; 49: 2679-85.
3. Simo R, Higuera M, Garcia-Ramirez M, Canals F, Garcia-Arumi J, Hernandez C. Elevation of apolipoprotein A-I and apolipoprotein H levels in the vitreous fluid and overexpression in the retina of diabetic patients. *Arch Ophthalmol* 2008; 126: 1076-81.
4. Simo R, Garcia-Ramirez M, Higuera M, Hernandez C. Apolipoprotein A1 is overexpressed in the retina of diabetic patients. *Am J Ophthalmol* 2009; 147: 319-25.
5. Eto M, Watanabe K, Sato T, Makino I. Apolipoprotein-E2 and hyperlipoproteinemia in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1989; 69: 1207-12.
6. Balson KR, Niall JF, Best JD. Glomerular lipid deposition and proteinuria in a patient with familial dysbetalipoproteinaemia. *J Intern Med* 1996; 240: 157-9.
7. Suzaki K, Kobori S, Ueno S, Uehara M, Kayashima T, Takeda H, et al. Effects of plasmapheresis on familial type III hyperlipoproteinemia associated with glomerular lipodosis, nephrotic syndrome and diabetes mellitus. *Atherosclerosis* 1990; 80: 181-9.
8. Crispin S. Ocular lipid deposition and hyperlipoproteinaemia. *Prog Retin Eye Res* 2002; 21: 169-224.
9. Haffner SM. Management of dyslipidemia in adults with diabetes. *Diabetes Care* 2003; 26 (Suppl 1): S83-6.
10. Popescu T, Mota M. Dyslipidemia and hypertension in patients with type 2 diabetes and retinopathy. *Rom J Intern Med* 2009; 47: 235-41.
11. Cusick M, Chew EY, Chan CC, Kruth HS, Murphy RP, Ferris FL 3rd. Histopathology and regression of retinal hard exudates in diabetic retinopathy after reduction of elevated serum lipid levels. *Ophthalmology* 2003; 110: 2126-33.
12. Gordon B, Chang S, Kavanagh M, Berrocal M, Yannuzzi L, Robertson C, et al. The effects of lipid lowering on diabetic retinopathy. *Am J Ophthalmol* 1991; 112: 385-91.
13. Waller S, Thyagarajan S, Kaplan F, Viljoen A. Dramatic resolution of massive retinal hard exudates after correction of extreme dyslipidaemia. *Eye (Lond)* 2009; 23: 738.
14. Ansquer JC, Foucher C, Aubonnet P, Le Malicot K. Fibrates and microvascular complications in diabetes—insight from the FIELD study. *Curr Pharm Des* 2009; 15: 537-52.

รายงานผู้ป่วยโรคเบาหวานและไขมันในเลือดสูงที่มีภาวะไขมันสะสมใต้จอตาพร้อมกับต้อหินชนิดหลอดเลือดแดงอกผิดปกติ เป็นอาการนำมาพบแพทย์

สุรสิทธิ์ สีนะวัฒน์, สุขุมล ธนไพศาล, สุพัฒน์ สีนะวัฒน์

ผู้ป่วยชายอายุ 50 ปี มาด้วยอาการตามัวลงทั้งสองข้างในระยะเวลา 5 เดือน ระดับการมองเห็นลดลงเหลือเพียงสามารถนับนิ้วได้ในตาขวา และมองเห็นเพียงแสงไฟในตาซ้าย แม้ตรวจพบหลอดเลือดแดงผิดปกติที่มุมตาของตาทั้งสองข้างแต่พบหลอดเลือดแดงผิดปกติที่ม่านตาพร้อมกับโรคต้อหิน ชนิดหลอดเลือดแดงผิดปกติในตาซ้ายเท่านั้น ตรวจจอตาพบไขมันสะสมใต้จอตาปริมาณมากทั้งสองตา ตาซ้ายพบหลอดเลือดแดงดำและขั้วประสาทตาชัด อีกทั้งยังพบคúmไขมันพิวหน่งที่หลังและแขนขา การตรวจเลือดพบระดับคอเลสเตอรอล 1,311 มิลลิกรัมต่อเดซิลิตร ระดับไตรกลีเซอไรด์ 6,356 มิลลิกรัมต่อเดซิลิตร ระดับน้ำตาลในเลือด 325 มิลลิกรัมต่อเดซิลิตรและระดับน้ำตาลสะสม 12.1 เปอร์เซ็นต์ ผู้ป่วยจึงได้รับการวินิจฉัยโรคไขมันในเลือดสูง และโรคเบาหวาน ระดับไขมันและน้ำตาลในเลือดลดลงอย่างมากหลังการรักษาด้วยยาฉีดอินซูลินและยาลดระดับไขมัน อย่างไรก็ตามระดับการมองเห็น ยังไม่ดีขึ้นแม้จะได้รับการรักษาด้วยการฉีดยา anti-VEGF และยาสเตียรอยด์เข้าม่านตาร่วมกับการยิงเลเซอร์แล้วก็ตาม

สรุป: การทำลายของ blood-retinal barrier จากโรคเบาหวานและการเปลี่ยนแปลงเมตาบอลิซึมของไขมันใน retinal pigment epithelium เป็นสาเหตุหลักของการเกิดโรคไขมันสะสมใต้จอตา อย่างไรก็ตามภาวะหลอดเลือดจอตาอุดตันอาจเป็นสาเหตุสำคัญของโรคต้อหินชนิดหลอดเลือดแดงผิดปกติในผู้ป่วยรายนี้
