Original Article - Clinical

Atypical Manifestations of Diabetic Retinopathy

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Introduction

The Organization of World Populations has reported a dramatic worldwide increase in the incidence of diabetes mellitus and its complications over the past decade [1]. Diabetic retinopathy (DR) is a common and well recognized but clinically varied complication of diabetes mellitus. We review in turn the inherent variability of the manifestations of diabetic retinopathy, systemic and ocular diseases that can affect the presentation of DR, and miscellaneous retinal findings that can occasionally be observed in patients with diabetes mellitus.

Inherent variability in Diabetic Retinopathy

Diabetic Disc Edema (diabetic papillopathy)

Diabetic papillopathy is described classically as a transient, unilateral or bilateral disc edema in individuals with long-standing diabetes mellitus and relatively good vision at presentation (Fig. 1). Diabetic papillopathy has been suggested to represent the extension of diabetic microangiopathy onto the optic nerve head [2]. Two large case series have each reported no association between the diagnosis of diabetic papillopathy and the patient age [2,3].

It is important to differentiate diabetic papillopathy from more serious disorders of the optic nerve. In bilateral cases, malignant hypertension and papilledema must be ruled out by blood pressure measurement and by neuroimaging followed by lumbar puncture, respectively. Nonarteritic anterior ischemic optic neuropathy is a common cause of optic disc edema, particularly in older patients. It can sometimes be quite difficult to distinguish from diabetic papillopathy [4,5•], leading Hayreh to suggest that diabetic papillopathy may be a mild form of nonarteritic anterior ischemic optic neuropathy [6]. Ischemic optic neuropathy is usually readily distinguished from diabetic papillopathy by the more profound level of vision loss and by the presence of a moderate to marked afferent pupillary defect. True neovascularization of the disc also needs to be distinguished from diabetic papillopathy, both by the orientation and location of the vessels - the telangiectatic vessels of diabetic papillopathy are arranged radially and lie within the substance of the disc - and by the degree of leakage evident on fluorescein angiography [2,3]. Rarely, true neovascularization of the disc may develop superimposed on diabetic papillopathy [2,7].

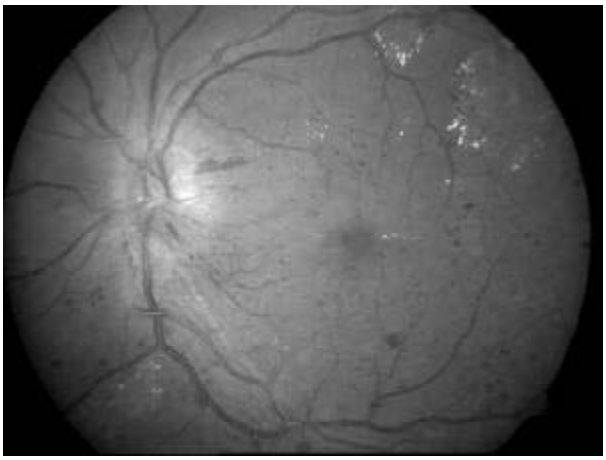

Fig : 1 Color photograph of the right fundus showing a hyperemic disc edema with telangiectatic disc vessels in the setting of non-proliferative diabetic retinopathy.

"Featureless Retina"

Occasionally, retinal neovascularization appears in patients with DR in the absence of intraretinal lesions that are usually considered to be typical of preproliferative retinopathy, including cotton-wool spots, dot-blot hemorrhages, and intraretinal microvascular abnormalities. Such "featureless" neovascularization may be explained by the transient nature of cotton-wool spots and/or by the fact that

dot-blot hemorrhages, microaneurysms, and intra retinal microvascular abnormalities tend to disappear in areas of extensive capillary closure [8]. Featureless retinas appear atrophic on careful inspection, and fluorescein angiography usually reveals extensive capillary nonperfusion, often with clinically undetected areas of neovascularization (Fig. 2).

Peripheral Abnormalities in Diabetic Retinopathy

A minority of patients with DR, perhaps 2 to 3%, show relative sparing of the posterior pole (Fig.3) [9,10]. Eyes in such patients often develop peripheral neovascularization, which can be easily missed. Neovascularization of the disc can also occur, even when the macula and peripapillary retina are well perfused [11]. Neovascular glaucoma and anterior hyaloidal fibrovascular proliferation are probably closely related to peripheral retinal ischemia [12,13]. Terasaki *et al.* reported an unusual fibrovascular ridge at the ora, seen intraoperatively in nearly half the eyes with proliferative diabetic retinopathy (PDR) and peripheral avascularity. The ridge is probably a precursor of anterior hyaloidal fibrovascular proliferation and was strongly associated by these investigators with the presence of anterior segment neovascularization [12,13]. Ishibashi *et al.* have reported peripheral new vessels growing from the choroid in an eye enucleated for PDR with neovascular glaucoma [14].

Florid Diabetic Retinopathy

Florid DR is a rare complication of severe diabetes mellitus, accounting for less than 1% of all cases of PDR [15,16]. Florid DR is characterized by bilateral, rapidly progressive, severe ischemic retinopathy associated with a high risk of blindness. Early recognition of this condition is therefore critical. Initially termed "diffuse capillary retinopathy" by Beaumont and Hollows [15], florid DR typically occurs in young, type 1 diabetic patients with long-standing and poorly controlled diabetes. It appears to affect women more often than men and is frequently associated with systemic complications [15,16,17]. The ophthalmoscopic diagnostic criteria include features characteristic of "aggravated very severe nonproliferative diabetic retinopathy," as defined by the authors, with or without neovascularization of the retina and/or optic disc, and a documented history of rapid progression [16]. Extensive subconfluent panretinal photo-coagulation with early vitrectomy when indicated may improve the prognosis in patients with florid DR, especially when compared with patients who undergo vitrectomy without previous photocoagulation [16,17].

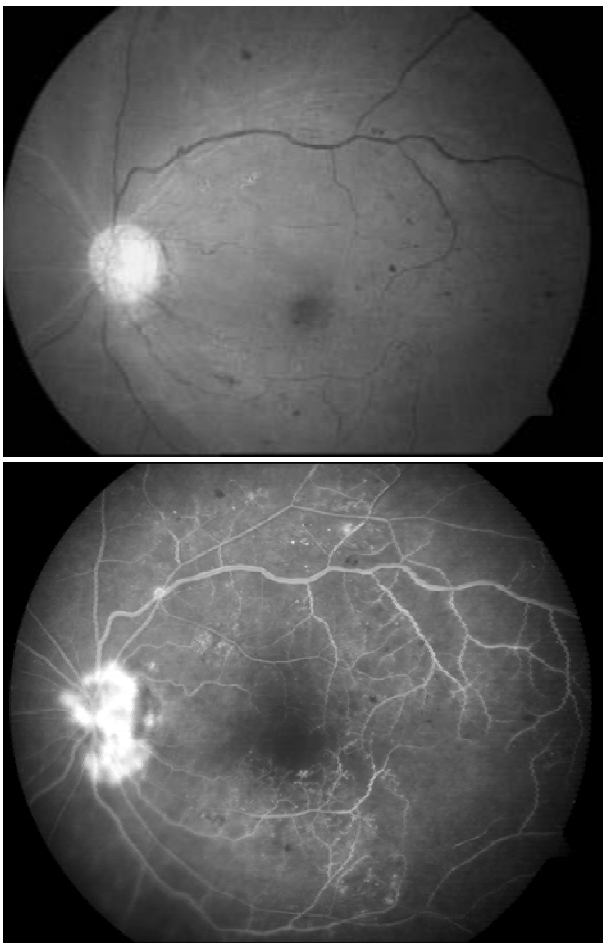

Fig 2 a. Color photograph of the left fundus showing apparently mild diabetic retinopathy changes with optic disc neovas cularization. Note the generalized retinal atrophy and marked arteriolar narrowing.
b. Fluorescein angiogram of the same eye demonstrating extensive capillary non-perfusion accompanied by leakage from the new vessels at the optic disc.

Diabetic Retinal Pigment Epitheliopathy

Diabetic macular edema is presumed to be primarily of retinal vascular origin. Weinberger *et al.* have demonstrated, however, an unusual form of diabetic

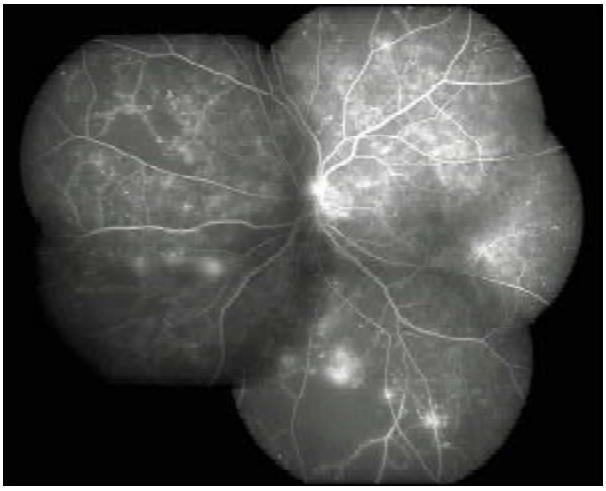

Fig 3 (A) Midphase fluorescein angiogram of the right eye showing the posterior pole with mild diabetic changes and no capillary non-perfusion.

maculopathy in which the retinal pigment epithelium also appears to play a key role [18]. The studied eyes showed minimal retinopathy with very few microaneurysms and no clinically significant macular edema, but angiograms revealed diffuse late-phase leakage from the macular retinal pigment epithelium. All eyes had excellent vision[18]. Animal studies using fluorophotometry support this notion that a disruption of the outer blood retinal barrier may contribute to the development of diabetic maculopathy [19].

Cilioretinal Artery and Diabetic Maculopathy

Knudsen and Lervang studied diabetic patients with a cilioretinal artery and asymmetric retinopathy [20]. The prevalence of dot-blot hemorrhages, hard exudates, and clinically significant edema were all increased in the eyes with a cilioretinal artery. The authors speculated that differences in perfusion pressure between the retina and the choroid, perhaps in combination with "substances" brought from the choroid to the macula by the cilioretinal artery, might somehow contribute to the asymmetry of the maculopathy in such patients.

Diabetic Tractional Papillopathy

Kroll *et al.* reported 17 patients with PDR who showed an isolated vitreous traction on the nasal aspect of the disc, optic disc pallor, reduced vision, and a subnormal visually evoked potential [21]. Other causes of visual loss were excluded. The explanation given for this constellation of findings was that stretching or kinking of the ganglion cell axons along with compromised blood flow caused by the traction resulted in a reversible impairment, of the papillomacular bundle function. Vitrectomy improved both vision and visually evoked potential parameters moderately. McLeod questioned the existence of diabetic tractional papillopathy as a distinct entity and cautioned against the need for surgery in such patients [22].

Atypical Cotton Wool Spots

Egerer and Freyler described four diabetic patients with cotton-wool spots ranging in size from 2 to 4 disc diameters [23]. These unusual lesions were reported to develop after a stenosis or total obstruction of a first order arteriole at the point of its emergence from the parent artery. There was an attempt at restoration of circulation by the surrounding arterioles and venules, the latter carrying a reversed blood flow. Arteriovenous communications along the perimeter of the cotton-wool patch were a prominent feature.

Foveal Neovascularization in Diabetic Retinopathy

Finkelstein *et al.* [24], and later Joondeph *et al.* [25], described an unusual presentation characterized by neovascularization at the perifoveal capillary ring. All patients described by these authors had long-standing, insulin-dependent diabetes mellitus. Most also had additional areas of neovascularization. The new vessels were nonprogressive and tended to be associated with good vision in spite of foveal capillary dropout. Joondeph *et al.* suggested that some degree of capillary dropout in the posterior pole was universal in advanced DR and that the resulting ischemia might have led to the formation of these anomalous perifoveal vessels.

Equatorial Fibrovascular Proliferation

Han *et al.*, in a retrospective analysis of diabetic vitrectomies, reported that 3% of their preoperative cases had unusual fibrovascular proliferation that was limited to the equatorial and preequatorial fundus in the absence of marked posterior traction, resulting in

recurrent vitreous hemorrhage and tractional detachments [26]. While it is possible that peripheral capillary nonperfusion might have caused these equatorial proliferations [10], the authors themselves quoted the use of previous photocoagulation, the location of arteriovenous crossings, and variations in the posterior cortical vitreous pocket as factors that may have contributed to the formation of equatorial fibrovascular proliferation [26]. This entity appears to be distinct from postvitrectomy anterior hyaloidal fibrovascular proliferation, from oral fibrovascular ridge formation, and from the formation of peripheral choriovitreal membranes [12,14,26].

Spontaneous Regression of Proliferative Diabetic Retinopathy

Bandello *et al.* described an unusual, spontaneous regression of retinal neovascularization in three nonpregnant women with type 1 diabetes and PDR, none of whom had any noteworthy change in the overall control of their diabetes [27]. Such regression was associated with a marked improvement in blood-retinal barrier breakdown and, remarkably, reperfusion of areas of capillary dropout documented by fluorescein angiography. The authors offered no explanation for the reversal. Spontaneous new vessel regression has rarely been reported in DR following an improvement in metabolic control [28] and at the conclusion of pregnancy [29]. Due to the extreme rarity of such an event, however, panretinal photocoagulation remains the standard of care for patients with PDR associated with high-risk characteristics.

Systemic Diseases Affecting Diabetic Retinopathy

Lipemic Retinopathy

When serum lipids, particularly triglycerides, increase substantially in a diabetic patient, a fundus picture described as "lipemic diabetic retinopathy," a milder variant of lipemia retinalis, may result. One study reported such findings in 2% of their diabetic patients [30]. In some instances, lipemic retinopathy can be severe enough to mimic a Coat's-like response (Fig. 4). Lipemia retinalis *per se* has also been described in a child with diabetic ketoacidosis [31]. Anecdotal evidence suggests that lipid-lowering drugs, particularly statins, can reduce the number and the extent of macular hard exudates in patients with DR. Reduced hard exudates may not, however, be associated with an improvement in vision [31,32,33].

Carotid Occlusive Disease

While an association between carotid occlusive disease and DR has been known for nearly 4 decades [34], the jury is out on its effect on DR. Gay and Rosenbaum first suggested that it imparted a protective influence on the progression of DR [34].

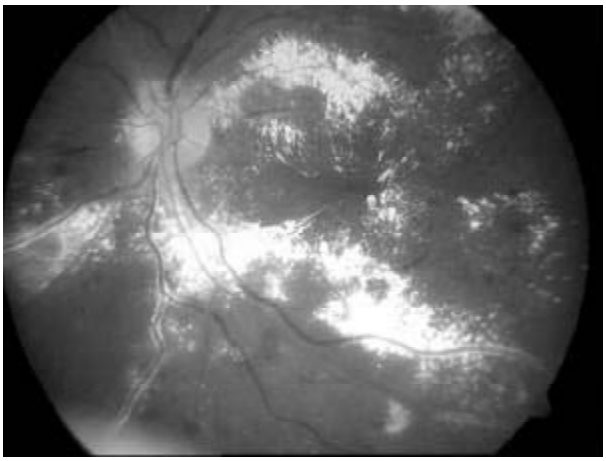

Fig.4 Fundus photograph of the left eye showing extensive accumulation of intraretinal hard exudates at the posterior pole.

Moss *et al.*, from the Wisconsin Epidemiological Study of Diabetic Retinopathy, also showed a significant association between low ocular perfusion pressure and incidence of DR in young diabetic subjects [35]. Duker *et al.,* however, disputed the protective effect of carotid occlusive disease against PDR [36]. Dogru *et al.* found carotid insufficiency on the same side as PDR in all their cases with asymmetric DR [37••]. Ino-ue *et al* suggested that eyes with ipsilateral carotid stenosis in effect had a macroangiopathy further worsening the retinal microangiopathy [38]. It makes intuitive sense that an ischemic influence like carotid occlusive disease should aggravate DR. When severe enough to result in ocular ischemic syndrome, it definitely does so, and it may sometimes be impossible to distinguish from PDR. It is important to recognize ocular

ischemic syndrome in DR because of the poor visual prognosis once rubeosis develops [38].

Ocular Conditions Affecting Diabetic Retinopathy

DR seems to show less progression in myopic eyes. Moss *et al.* demonstrated that myopia of -2 diopters or less protected against the development of PDR in youngeronset diabetes mellitus [35]. Dogru *et al.* reported similar results in a small cohort of patients with non–insulindependent diabetes mellitus [37••]. Baker and associates suggested that the protective effect against PDR was significant only in HLA-susceptible individuals. Proposed mechanisms of protection have included decreased ocular blood flow, thinning of retina thereby increasing oxygen diffusion [39], and improved pressure dissipation by the arteriolar tree [40]. Eyes with DR probably have shorter axial lengths than eyes without retinopathy, even in nonmyopic patients with diabetes [41].

Glaucoma has long been suspected to reduce the prevalence and severity of DR. The mechanism of protection in patients with glaucoma may be related to the loss of metabolic activity with decreasing numbers of viable ganglion cells or to reduced vascular perfusion due to an elevated intraocular pressure [42]. The latter hypothesis is supported by a report of progression of DR following filtration surgery in diabetic patients with glaucoma [43]. Of note, however, Moss *et al.* found no protective effect of glaucoma in their cohort of patients with DR [35].

Dellaporta *et al.* described 16 eyes with optic atrophy and DR. Retinopathy regressed or disappeared in all eyes over a 22-month follow-up [44]. The protective effect of optic atrophy may be due to reduced metabolic demand of the retina as has been suggested in glaucoma [37••]. The role of vitreoretinal traction in the evolution of DR is well established. Occurrence of total posterior vitreous detachment in an eye with early nonproliferative DR may prevent the progression of retinopathy [37••,45].

Rods have the highest metabolic rate of any cell in the body and remove considerable amounts of oxygen from the inner retina, rendering it almost pathologically anoxic during dark adaptation. Degeneration of rods in retinitis pigmentosa may therefore increase the oxygen levels in the inner retina and prevent the release of vasogenic cytokines known to be important in the pathogenesis of DR. Arden, in an internet-based survey of 55 retinitis pigmentosa patients with diabetes mellitus, found that none had DR [46•]

Browning *et al.* observed two patients with unilateral amblyopia and fellow-eye PDR for at least 2 years; the amblyopic eye maintained a stable background retinopathy [47]. The protective effect of amblyopia might be explained by a decreased blood flow [48] and/or reduced oxygen demand [47].

Miscellaneous

Asymmetric Diabetic Retinopathy

Asymmetric DR has been defined as PDR in one eye and nonproliferative DR or no retinopathy in the

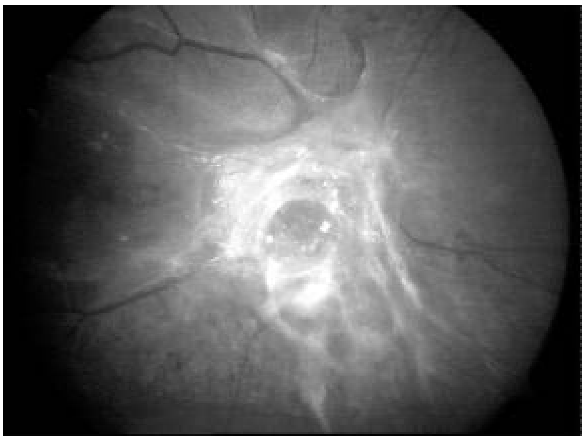

Fig. 5 Fundus photograph of the right eye showing exten- sive fibrous proliferation at the optic disc, & a tractional retinal detachment involving the macula.

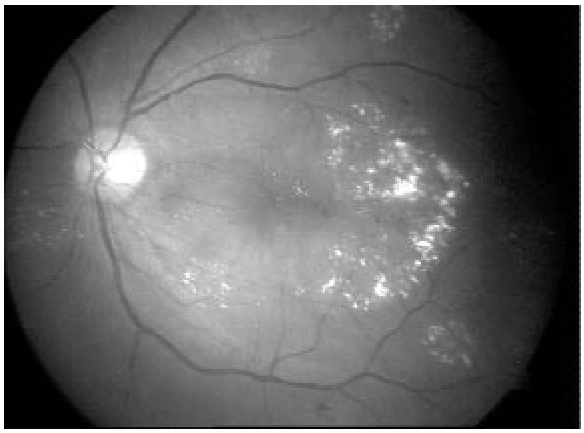

Fig. 6 Fundus photograph of the fellow eye showing non-proliferative diabeticretinopathy.

fellow eye persisting for more than 2 years [37••,47] (Fig. 5). Approximately 5 to 10% of diabetic patients have been reported to have asymmetric DR [36]. However, before diagnosing this condition, it is critical not to mistake a featureless retina for nonproliferative DR (q.v.). A host of factors have been suggested to contribute to asymmetry, including cataract surgery and the presence of a branch retinal vein occlusion, both of which tend to facilitate the progression to DR. Conversely, chorioretinal scarring, optic atrophy, posterior vitreous detachment, myopia, and glaucoma tend to lessen the progression of disease. While the effect of mild carotid insufficiency on the progression of DR is not clear, the presence of severe stenosis can be associated with worsening of retinopathy on the side of the occlusion [47].

Vision through Vitreous Hemorrhage

Espaillat *et al.* reported an unusual case of a type 1 diabetic woman who presented with dense vitreous hemorrhage and a vision of hand motions in the left eye [49]. With careful head positioning, the visual acuity dramatically improved to 20/40 though a small central island. Fundus examination showed a central clear opening in the posterior hyaloid, confirmed to be a Weiss ring by ultrasonography. The authors explained that in cases of only intragel vitreous hemorrhage, the blood might not fill the Cloquet canal, providing an optically clear path through the Weiss ring.

Conclusion

The importance of studying the atypical manifestations of DR is best appreciated by recapitulating the landmark observation of Aiello *et al.* to the effect that the eyes with extensive chorioretinal scarring from any cause experience a markedly low prevalence and severity of DR. This observation led to an attempt to induce the same effect iatrogenically by "panretinal photocoagulation" and formed the basis of the trend-setting clinical trials for the treatment of DR [42]. The identification and better understanding of some of the lesser known features of DR may similarly open up the possibilities for research into newer treatment modalities for the diabetic retinal disease.

Acknowledgments

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