

Featureless retina in diabetic retinopathy: Clinical and fluorescein angiographic profile

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Purpose: “Featureless retina” (FLR) has been only briefly mentioned in textbooks; this deceptively benign appearance of diabetic retinopathy (DR) merits a detailed description. Here we report the clinical profile, diagnosis, and management of FLR. **Methods:** The case records of consecutive type 2 diabetic patients clinically diagnosed as FLR were reviewed. The case selection was based on suggestive signs (white thread-like arterioles and atrophic retina), asymmetric presentation of DR, and fluorescein angiographic (FA) demonstration of retinal capillary nonperfusion (CNP) with/without proliferative disease (PDR). Panretinal photocoagulation (PRP) was performed as needed. The extent of CNP was correlated with diabetic macular ischemia (DMI) and neovascularization on FA, and DMI was correlated with best-corrected visual acuity using Pearson Chi-square test ($P < 0.05$). IBM SPSS Statistics 26 was used for analysis. **Results:** Out of 46 patients, 21 (46%) patients had bilateral and 25 (54%) had unilateral involvement (67 eyes with FLR). PDR was clinically discernible in two (3%) eyes; 65 (97%) eyes had clinical features of mild-moderate NPDR. However, FA revealed extensive CNP areas in 49 (73%) and PDR in 59 (88%) eyes. DMI was found in 83% of the eyes which had best-corrected visual acuity $< 6/12$; this association was statistically significant ($P = 0.024$). Fifty-seven (85%) eyes underwent panretinal photocoagulation (PRP) for extensive CNP or PDR. **Conclusion:** Behind the mild-moderate clinical profile of FLR lay extensive CNP and PDR, which were unmasked by FA, with a complete overhaul of the treatment and follow-up.

Key words: Capillary nonperfusion, featureless fundus, featureless retina, proliferative diabetic retinopathy

Diabetes mellitus is a global pandemic, with India having a lion’s share of 77 million cases among its adult population (20–79 years), a number that is likely to double over the next 25 years.^[1] Since the discovery of insulin, the prolonged lifespan of diabetic subjects has ironically opened the Pandora’s box of diabetic retinopathy (DR), nephropathy, and neuropathy, with their multiple attendant complications, including diabetic blindness.^[2] The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that with regular follow-ups and adequate treatment, up to 98% of diabetic blindness can be prevented.^[3] A key element of regular follow-ups is timely screening and accurate staging of DR severity so that the need for follow-up and early treatment can be determined. While the initial comprehensive grading by ETDRS has been substantially simplified for the practicing physician,^[4,5] the increasing prevalence of diabetic retinopathy keeps unveiling an ever wider variety of uncommon presentations that flummox and mislead us.^[6] One such presentation is *featureless retina*, only briefly touched upon in Ryan’s textbook of Retina; the description has practically remained unchanged over several editions,^[7] and has never been specifically described in the peer-reviewed literature. We present our clinical experience with diagnosis, investigation, and management of this poorly

known and probably underdiagnosed clinical presentation of the advanced stages of DR.

Methods

We reviewed the case records of adult patients with type 2 diabetes mellitus confirmed by a physician at a tertiary eye care center and selected the consecutive cases diagnosed as featureless retina (FLR) by an experienced grader. Diabetic retinopathy was graded on the basis of a simplified ETDRS severity scale: no retinopathy, mild, moderate, or severe nonproliferative DR (NPDR) and proliferative DR (PDR).^[5] FLR was diagnosed in cases with apparently mild-moderate NPDR or early PDR in one or both eyes of a diabetic patient with suggestive clinical signs: white, thread-like arterioles and atrophic or thinned-out appearance of retina [Fig. 1a and b].^[6,7] FLR was proactively suspected when DR was clinically observed to be asymmetric between the two eyes of a diabetic subject: PDR in one eye and mild-moderate NPDR in the other eye with/without the aforementioned characteristics of FLR.^[6] Fluorescein angiography (FA) was performed to look for the macular perfusion and midperipheral capillary closure in all the enrolled cases [Fig. 2].

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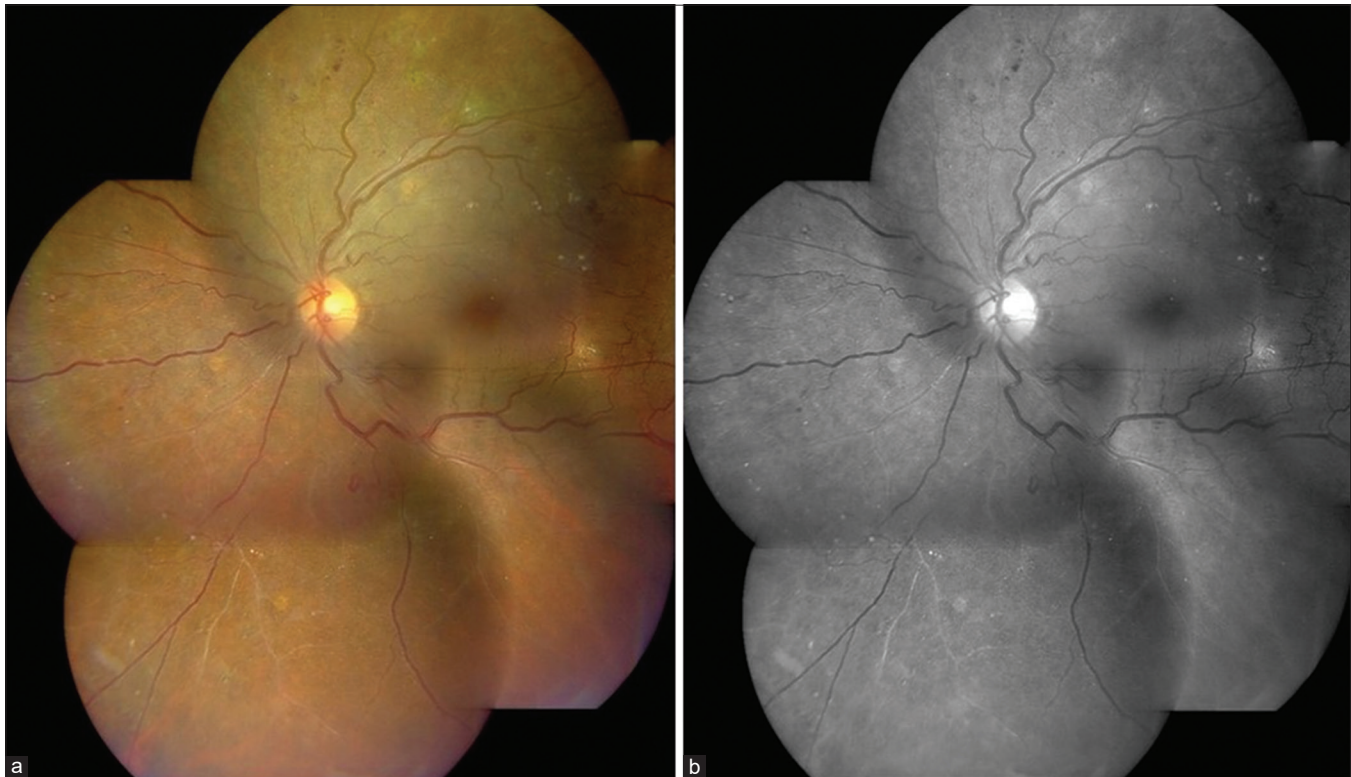


Figure 1: Featureless retina (a and b) The montage fundus photograph of the left eye shows a clinical severity grading of mild nonproliferative diabetic retinopathy. The diagnostic clues for FLR are arteriolar narrowing and sheathing inferiorly and inferonasally, and attenuated, featureless appearance of the background retina: red-free imaging highlights these subtle features (b)



Figure 2: Fluorescein angiography (FA) of FLR: FA reveals extensive capillary nonperfusion in the inferior, nasal, and superior midperiphery with multiple leaking new vessels at the border of nonperfused with perfused retinal capillaries. Note that capillary closure almost exactly corresponds to the sheathed arterioles and atrophic retina

The exclusion criteria included clinically apparent high-risk features (HR-PDR) such as large, elevated new vessels, preretinal

hemorrhage; features of severe NPDR such as extensive dot-blot hemorrhages, venous beading, or intraretinal microvascular abnormalities (IRMA); involucional or quiescent PDR with white fibrovascular proliferation at the optic disc (FPD) or elsewhere (FPE) with/without spontaneously settled tractional retinal detachments and epiretinal membrane^[2,7,8]; post-scatter photocoagulation regression of PDR; complete posterior vitreous detachment, or degenerative conditions such as high myopia, open-angle glaucoma, and retinitis pigmentosa, which slow down the progression of DR;^[6] and absence of good-quality fluorescein angiography (FA) records for the patient or an increased arteriovenous transit time (suggestive of ocular ischemic syndrome) on FA. Finally, the presence of any coexisting disease such as retinal vein occlusion, uveitis, retinal vasculitis, or recent intraocular surgery (which could accelerate/complicate/mimic DR or FLR) was carefully excluded.

On FA, we assessed the extent of midperipheral capillary nonperfusion (CNP) areas, status of foveal avascular zone (FAZ), and the leakage from new vessels on the disc or elsewhere (NVD/NVE). The highest-quality capillary phase of FA was used to assess CNP areas and FAZ. We quantified the severity of midperipheral retinal ischemia as disc areas (DA) of CNP according to the Central Retinal Vein Occlusion Study (CVOS) criteria into two groups: CNP ≥ 10 DA and CNP < 10 DA.^[9] Diabetic macular ischemia (DMI) was defined as moderate-severe irregularities of the FAZ as described by Bresnick *et al.* (e.g., FAZ enlarged ≥ 1000 μ , notched, or bordered by microaneurysms, telangiectasia, or pruned arterioles).^[10] Active NVD and NVE were identified by evidence of extramural leakage on FA in late phases. The main outcome

measures were the clinical picture in FLR and the angiographic features. The secondary outcome measure was the correlation of visual status with FA findings.

Pearson Chi-square test was used to correlate the extent of CNP with DMI and NVD/NVE on FA, and to correlate DMI with best-corrected visual acuity, at the significance level of $P < 0.05$. IBM SPSS Statistics ver. 26 statistics software was used for analysis. The study was conducted in accordance with the principles laid down for human research in the Helsinki Declaration. The approval of the Institutional ethics committee was waived for this retrospective review of records of routine investigations on diabetic patients.

Results

Forty-six type 2 diabetic patients fulfilled the inclusion criteria. There were 34 men and 12 women with a mean age of 57.35 ± 9.15 years (range: 38–78 years). Mean duration of diabetes was 13.07 ± 8.91 years (range: 1–35 years). Associated hypertension (HT) was present in 32.6% of patients, ischemic heart disease (IHD) in 6.5%, hyperlipidemia in 19.5%, and chronic renal failure (CRF) in 13% of patients. Twenty-one (45.6%) patients had bilateral appearance of FLR, whereas 25 (54.4%) patients had unilateral involvement; a total of 67eyes were included in the study.

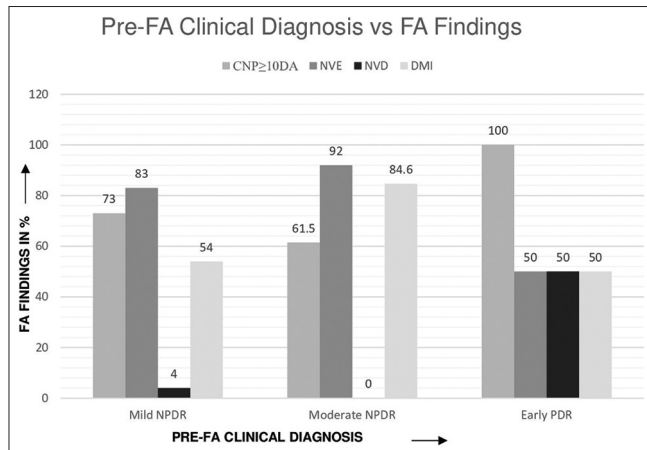


Figure 3: Distribution of fluorescein angiographic findings against pre-angiography clinical diagnosis in Featureless Retina: While FA findings are obvious in PDR, they reveal an alarmingly high percentage of extensive CNP, NVE/NVD, and macular ischemia in eyes clinically graded as mild-moderate NPDR. FA: Fluorescein angiography, NPDR: Nonproliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, CNP: Capillary nonperfusion, DA: Disc area, NVE: Neovascularization elsewhere, NVD: Neovascularization at optic disc, DMI: Diabetic macular ischemia

The fundus picture suggestive of mild NPDR was observed in 52 eyes, moderate NPDR in 13 eyes, and early PDR in two eyes. Fifty-two (78%) eyes showed characteristic sheathed vessels with atrophic appearance of retina [Table]. The fundus findings of the fellow eye of the unilateral (25) cases were noted as no DR in one (4%), moderate NPDR in four (16%), early PDR in seven (28%), and HR-PDR in 13 (52%) eyes.

FA revealed CNP areas ≥ 10 DA in 49 (73%) eyes, NVE in 56 (83.6%), NVD in three (4.5%), and DMI in 41 (61%) eyes. Both CNP ≥ 10 DA and MI were seen in 45% (30/67) eyes; however, their association was not statistically significant ($P = 0.993$). Similarly, both CNP ≥ 10 DA and NVD/NVE were seen in 63% (42/67) eyes, but this association did not reach statistical significance ($P = 0.328$) either [Table 1]. Sixteen eyes showed NVE, and one eye showed NVD on FA in the absence of CNP ≥ 10 DA.

Both the eyes with FLR and clinically evident PDR showed extensive CNP (≥ 10 DA) on FA, besides the presence of NVD/NVE. Remarkably, the 65 eyes with pre-FA diagnosis of mild-moderate NPDR revealed extensive CNP in 46 (>70%) eyes and had macular ischemia as or more commonly as pre-FA PDR. If we add the number of eyes that showed NVE/NVD, close to 90% of eyes jumped into the severe or proliferative category of DR after FA [Fig. 3]. Indeed, 57 (85%) eyes underwent panretinal photocoagulation (PRP) for CNP ≥ 10 DA or NVD/NVE; seven (10.4%) eyes underwent focal photocoagulation for clinically significant DME (CSME).

Best-corrected Snellen visual acuity (BCVA) in the study eye ranged from 6/6 to 2/60. Of the 67 eyes, 49 eyes had BCVA of 6/6–6/12, 15 eyes had BCVA of 6/18–6/36, and three eyes had BCVA worse than 6/36. Eighteen out of 67 (27%) eyes had BCVA $< 6/12$, of which 15 (83%) eyes showed presence of DMI on FA; this association of macular ischemia with BCVA $< 6/12$ was statistically significant ($P < 0.05$, Table 1).

Discussion

We present 46 type 2 diabetic patients (67 eyes) with a hitherto overlooked feature of DR: featureless retina. New vessels were clinically discernible in only two (3%) eyes, whereas 65 (97%) eyes were suggestive of mild-moderate NPDR. This clinically innocuous appearance was misleading: FA revealed extensive capillary closure in almost 3/4th of the eyes and extraretinal neovascularization in close to 90% of eyes. Macular ischemia was observed in more than 60% eyes and in more than 80% of the eyes with subnormal vision.

The textbook description of FLR highlighted the paradox of progressive capillary closure: the pathological basis of fundus changes in DR.^[7] Though DR severity increases with the extent of CNP,^[11] extensive capillary closure sometimes obliterates

Table 1: Clinical characteristics, visual status, and correlation with macular and midperipheral ischemia in featureless retina

Pre-FA Clinical Picture	n (%)	BCVA	n (%)	Angiographic Features	n (%)	Correlation (P)
Mild NPDR	52 (77.6)	$\geq 6/12$	49 (73)	CNP ≥ 10 DA	49 (73)	CNP ≥ 10 DA and DMI (0.993)
Mod NPDR	13 (19.4)	$< 6/12$	18 (27)	NVE	56 (83.6)	CNP ≥ 10 DA and NV (0.328)
Early PDR	2 (3)			NVD	3 (4.5)	DMI and vision $< 6/12$ (0.024)*
Thread-like Arterioles**	52 (78)			DMI	41 (61)	

FA: Fluorescein angiography, BCVA: Best-corrected visual acuity, NPDR: Nonproliferative diabetic retinopathy, CNP: Capillary nonperfusion, DA: Disc area, DMI: Diabetic macular ischemia, Mod: Moderate, NVE: Neovascularization elsewhere, PDR: Proliferative diabetic retinopathy, NVD: Neovascularization at disc. *statistically significant at $P < 0.05$; **Thread-like arterioles could accompany any of the three stages of DR (mild-moderate NPDR/PDR)

IRMA and blot hemorrhages, and reduces arterioles to white thread-like structures. However, areas of FLR were illustrated as a local anomaly adjacent to severe or high-risk diabetic changes.^[7] When the appearance of FLR is widespread with no obvious clues to an underlying PDR—as we commonly observed in this case series—the risk of underestimation of DR severity becomes much higher. While nearly all the eyes in our series were clinically identified as mild-moderate NPDR, 85% of them required PRP for extensive CNP or FA-proven PDR (as recommended in type 2 diabetics).^[2,12] Even if PRP were to be deferred in these cases as they did not have traditional high-risk PDR, they must be monitored closely, unlike mild-moderate NPDR, which only requires a follow-up at 6–12 months.^[2]

We suspected FLR primarily in diabetics with asymmetric severity of DR in the two eyes. DR *per se* rarely presents with significant bilateral asymmetry.^[6,11] Though several ocular and systemic conditions and pathologies can potentially accelerate or slow down the progression of DR and cause asymmetric presentation, they can generally be ruled out with meticulous examination (*supra vide*).^[6] FLR should be added to the list of such atypical presentations and proactively looked for. Unlike the aforementioned pathologies, FLR does not lead to a truly asymmetric presentation: the post-FA severity of disease was symmetrically advanced in nearly 90% of the patients in this series. We also had close to half of the FLR cases presenting with a bilaterally bland picture. This is a particularly precarious situation where only a high level of suspicion, a proactive search for thread-like arterioles, and a low threshold for FA (or its noninvasive alternatives, if available) can help in clinching the crucial diagnosis. Besides arteriolar attenuation, one can look for retinal thinning and unexplained subnormal vision, especially in presence of minimal DR in a patient with a long history of uncontrolled diabetes.

The ETDRS severity scale for grading the lesions of DR is based purely on clinical examination and stereo fundus photography. FA is not recommended except to assess macular status and treatment.^[2] We found a high percentage of DMI in this study, in line with the predominance of advanced DR as revealed by FA; DMI was significantly associated with poor vision, as shown by others.^[10,13,14] However, we did not find a significant association between macular and midperipheral ischemia, probably because we used conventional FA and not ultra-widefield imaging (UWF-FA), limiting our assessment of peripheral CNP. There is a dichotomy in literature in this regard: UWF-FA reportedly revealed a significant association of macular ischemia with peripheral ischemia^[13]; but a more recent report employing both UWF-FA and noninvasive swept-source OCT angiography (UWF SS-OCTA) showed no such association, like us.^[14] Indeed, the gold standard ETDRS grading system is probably due for an update,^[15] both due to the frequency of DR changes outside the posterior 30-degree fields and because the clinically observed changes do not always follow a set temporal sequence, as we also observed in our case series.

Shimizu *et al.* discovered by conventional FA that retinal midperiphery, and even periphery, was actively involved in DR progression well before the redoubtable ETDRS severity scale was published^[11]; this fact was recently re-emphasized by

the researchers from Beetham Eye Institute.^[15,16] The stalwarts chairing the major DR trials also acknowledged the significance of CNP outside the ETDRS fields and made a passing mention of FLR as one of its markers.^[17]

There is an interesting analogy of FLR to be found in the stage 3 retinopathy of prematurity, observed with improved survival rates of extremely low birth weight infants, who sometimes show a “deceptive featureless” junctional area between the vascularized and avascular retina revealed by FA.^[18,19] This finding poses a serious threat to vision, like FLR, and requires early and urgent photocoagulation without waiting for the development of threshold disease.^[18]

The cross-sectional nature of this study precluded any prognostication on the natural history of FLR by further expansion of capillary dropout and its implications. We did not perform OCT consistently through this series. OCT was not essential because of the observed low frequency of CSME (10%) in FLR, probably secondary to loss of leaking microaneurysms from extensive capillary closure.^[7] Therefore, we could not correlate FLR or macular ischemia with anatomical changes such as outer retinal disruption.^[20] Noninvasive imaging tools such as UWF OCT angiography were not used either; it could have depicted the deep vascular plexus abnormalities in macular and retinal ischemia, which could correlate better with disruption in photoreceptor anatomy and function. Due to small number of cases, the systemic parameters such as cardiovascular status, HbA1C, lipid levels, or renal function could not be correlated with macular or retinal ischemia in this case series, though some of them (e.g., renal failure) might have a bearing on macular and retinal ischemia.^[16,21] Blood-flow parameters such as increased central retinal artery resistance index and decreased peak systolic velocity of internal carotid artery have been reported to cause asymmetric presentation of diabetic macular edema and retinopathy.^[22] However, the literature is equivocal about the exact nature of carotid vascular parameters associated with the presence or severity of DR as most of the studies have been cross-sectional.^[23] We performed Doppler imaging of the internal carotid artery only in the cases with angiographic features of ocular ischemic syndrome, which was an exclusion criterion (*supra vide*), and therefore could not correlate this parameter with asymmetric DR in this series. These shortcomings need to be addressed by a larger, longitudinal study of FLR with noninvasive wide-angle diagnostic imaging and a more detailed systemic assessment to assess its natural course and long-term prognosis.

Conclusion

Despite the abovementioned limitations, this pilot study attempts to detail the deceptively benign clinical features of FLR and the underlying high-risk features such as extensive CNP and proliferative disease, laid bare by the simple and universally available investigation of FA. It is possible that this entity may not be as uncommon as reflected by the lack of literature. We hope to sensitize the ophthalmologists involved in diabetic eye care to the possibility of FLR, suspect it proactively in asymmetric DR or in presence of suggestive clinical presentation, and look for retinal ischemia by FA for further intervention and visual prognostication.

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Conflicts of interest

There are no conflicts of interest.

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