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Clinical Presentations and Pathological Correlates of Retinopathy

Toke Bek

Department of Ophthalmology, Århus University Hospital, Århus, Denmark

Abstract

Diabetic retinopathy consists of a variety of morphological lesions in the retinal fundus related to disturbances in retinal blood flow. In this chapter, these clinical manifestations of diabetic retinopathy will be described, and the background and development of each individual lesion type and combinations of different lesion types will be discussed in relation to relevant theories and working hypotheses for the pathophysiology of the disease. Finally, the implications for central and peripheral vision of each lesion type occurring as part of diabetic retinopathy will be discussed.

Diabetic retinopathy is a frequent cause of blindness among young adults in the industrialised countries, and with the current epidemic of especially type 2 diabetes mellitus sweeping the Western world, diabetic complications including retinopathy can be expected to become even more frequent in the future [1].

The initial sign of diabetic complications in the retina is disturbances in visual function as evidenced by changes in the oscillatory potential of the electroretinogram [2], and these early functional changes constitute a risk factor for later development of central visual loss. However, paradoxically diabetic retinopathy is not diagnosed and monitored on the basis of functional changes in the retina, but on the basis of its morphological appearance as studied by ophthalmoscopy or fundus photography.

This appearance can be divided into:

1 Early changes that are reversible and do not threaten central vision. These changes are termed simplex retinopathy or background retinopathy, alluding to the fact that the lesions remain in the eye background.
2 Later vision-threatening changes that may assume one or both of two forms:
   a Diabetic maculopathy with retinal exudation and oedema that extends to the foveal region and threatens central vision.
   b Proliferative diabetic retinopathy which is growth of new vessels from the larger retinal venules. These new vessels may cause visual loss by spontaneous haemorrhage into the vitreous body or by inducing retinal detachment due to traction from connective tissue in the new vessels.

It is the detection of morphological lesions not appreciated by the patient that renders diabetic retinopathy suitable for screening by funduscopic inspection [3]. The clinical appearance of diabetic retinopathy has inspired a number of working

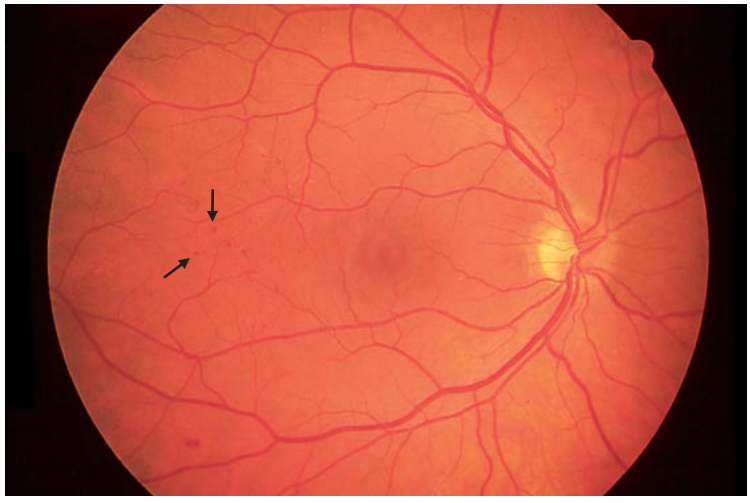

Fig. 1. Microaneurysms and haemorrhages temporal from the fovea (arrows).

hypotheses and methodological approaches for understanding the disease, based on the fact that the observed morphological lesions are related to disturbances in retinal blood flow. These disturbances include both hyperperfusion as a consequence of reduced tone in the retinal resistance vessels, which is most prominent in the macular area, and hypoperfusion as a consequence of capillary occlusion, which is most pronounced in the peripheral retina. The experimental approaches for studying these mechanisms are diverse and will be treated in more detail in other chapters of this volume.

In this chapter, the clinical manifestations of diabetic retinopathy will be described, and the background and development of each individual lesion type and combinations of different lesion types will be discussed in relation to relevant theories and working hypotheses for the pathophysiology of diabetic retinopathy.

Morphological Lesions

Microaneurysms and Haemorrhages

The initial sign of diabetic retinopathy is small red dots in the fundus background, typically located temporally from the foveal area [4], from where the lesion may spread to other parts of the macular area and the retinal periphery (fig. 1). Generally, the density of red dots reflects the density of the retinal capillary system which is highest in the macular area apart from the foveal avascular zone, and decreases towards the retinal periphery. The red dots occur together with retinal hyperperfusion and may represent microaneurysmatic dilations of the retinal capillaries or small haemorrhages resulting from localised ruptures of the retinal capillaries. By definition, the diameter of a microaneurysm is less than 100 μm, but most frequently the diameter of the lesion is not larger than 10–20 μm [5]. The differentiation of a microaneurysm from a small well-defined dot haemorrhage cannot be done on the basis of ophthalmoscopy alone, but requires fluorescein angiography by which a microaneurysm fills with fluorescein, whereas a haemorrhage remains dark [6]. The appearance of a haemorrhage often differs from that of a microaneurysm because the haemorrhage distributes around the surrounding anatomical structures. This is most clearly observed near the optic disk where haemorrhages may be arranged in flame-shaped lines

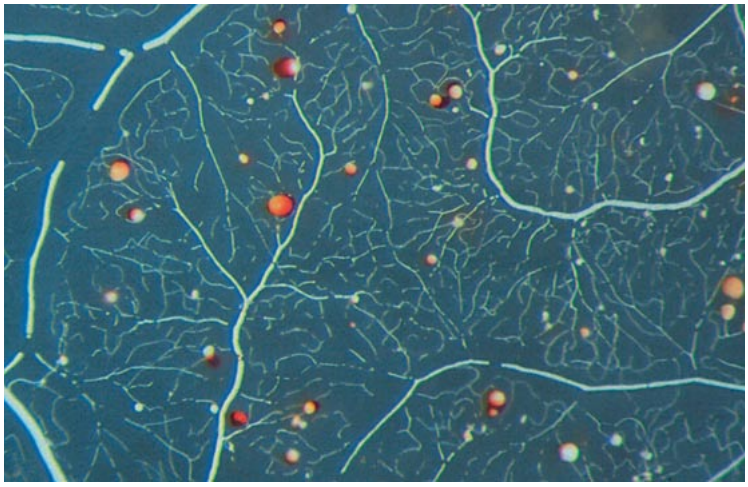

Fig. 2. Cast of human diabetic retinal capillary bed with organising microaneurysms. The red cap seen around the white casting material in the microaneurysms represents erythrocytes trapped in the thrombotic tissue growing from the cap of the lesions.

around the retinal nerve fibres. Furthermore, haemorrhages often become larger than microaneurysms or display an unsharp delimitation due to partial resorption. However, a differentiation of microaneurysms from dot haemorrhages does not have any practical implications since the two lesion types share a common pathophysiological background and have the same clinical significance.

The number of microaneurysms and haemorrhages is an indicator of the risk of further progression of diabetic retinopathy. Thus, it has been shown that the presence of a few red dots implies the same risk of progression of diabetic retinopathy as no lesions, and the risk of developing retinopathy increases with the number of red dots in the fundus [7–10]. Similarly, it has been shown that the visual prognosis after retinal photocoagulation is better when the treatment results in a reduction in the number of red dots to ≤4, than when this goal is not reached [11]. The number of microaneurysms and haemorrhages increases in parallel with the development of diabetic retinopathy, typically over years to decades [9]. However, the presence of a certain number of lesions covers a dynamic pattern with considerable turnover of lesions. Thus, fundus photographs taken repeatedly with 1-week intervals may often show the same number of lesions; however located at a new position from one examination to another, indicating a continuous new formation and resorption of the lesions [12].

The pathophysiology underlying the turnover of microaneurysms and haemorrhages is different. Thus, the formation of a microaneurysm starts with a localised dilation of a retinal capillary, probably secondary to both an increased hydrostatic pressure in the vessels and weakening of the structure of the capillary wall [5, 6, 13]. Subsequently, the microaneurysm gradually fills with thrombotic material (fig. 2) and undergoes organisation [14], during which the haemoglobin in the erythrocytes that have become trapped in the microaneurysm will be resorbed and the thrombotic mass will become invisible. The vascular wall remains thickened at the location of an organised microaneurysm, which implies that new microaneurysms are not formed at the same position. Therefore, it is a misconception of the natural history of diabetic retinopathy when it is recommended to eliminate microaneurysm by focal photocoagulation. The lesion will disappear

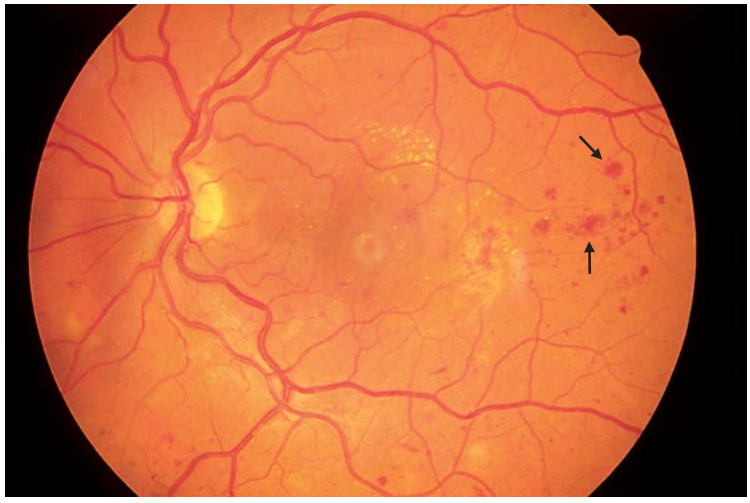

Fig. 3. Larger blot haemorrhages temporal from the fovea (arrows).

anyway. A possible positive effect on retinopathy is not due to the elimination of the microaneurysm, but to the more unspecific effect of outer retinal damage which is seen after photocoagulation in general. An organised whitish microaneurysm located in the centre of a haemorrhage may have an appearance similar to the hat batch named a cocarde. However, cocarde lesions may also develop secondary to other systemic and retinal diseases and do not play a specific diagnostic or prognostic role in diabetic retinopathy.

Retinal haemorrhages display a dynamic pattern of development which has two forms. One pattern is the formation and resorption of haemorrhages at the same location from time to time in so-called hot spots, indicating repetitive stress on the same retinal vessel. The other pattern consists of haemorrhages that develop at different locations from time to time in the retina, indicating that the areas where the capillary network is stressed varies from place to place.

Smaller dot haemorrhages are differentiated from larger blot haemorrhages on the basis of whether the diameter is smaller or larger than the diameter of the temporal arterioles at the crossing of the optic disk (fig. 3). The presence of a few blot haemorrhages alone is not a risk factor for progression of retinopathy. However, the presence of many blot haemorrhages distributed in clusters temporally in the macular area indicates severe peripheral ischaemia and that retinopathy has progressed to a pre-proliferative stage [15]. A special type of blot haemorrhage with the same prognostic significance as cluster haemorrhages develops from the perifoveal capillaries to extend over the foveal area and reduce visual acuity. Foveal haemorrhages always resolve spontaneously and result in an almost normalisation of central vision. These lesions are one of the few manifestations of diabetic retinopathy where a subjective symptom of a potentially vision-threatening retinopathy may encourage the patient to seek an ophthalmologist [15].

Exudates, Blood-Retina Barrier Leakage and Retinal Oedema

Retinal exudates are precipitations of plasma protein that have leaked from the retinal vessels [16, 17]. The typical 'hard' exudate appears as a sharply delimited whitish lesion in the surrounding reddish retina. The typical exudate has approximately the size of a microaneurysm, but the

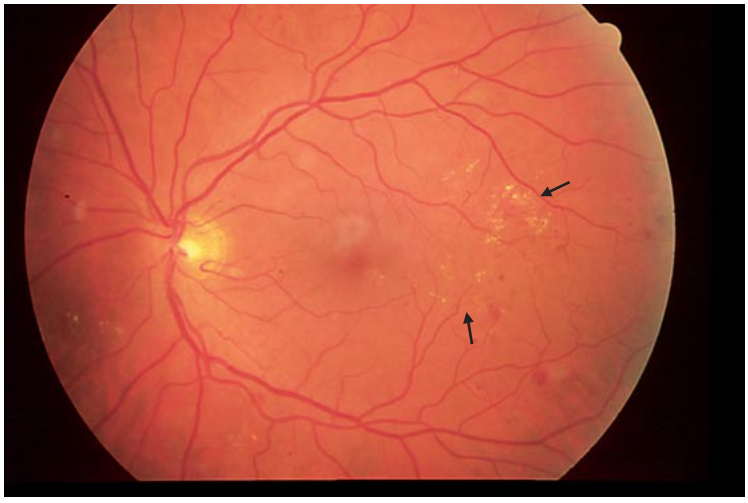

Fig. 4. Hard exudates in the macular area, some of which are forming exudate rings (arrows).

lesion may expand and merge with neighbouring lesions to form larger conglomerates of exudates. Exudates may occur as solitary lesions, in groups, or arranged in a circinate pattern concentrically around a single leakage point to form so-called exudate rings (fig. 4). Frequently, the first indication of a weakness of the microvasculature leading to leakage will be the occurrence of a dot haemorrhage that may have resorbed totally or partially when the exudate ring is observed concentrically around the haemorrhage.

Due to the occurrence of exudate rings around single leakage points, it is assumed that exudates represent precipitation lines located at a distance from the leakage point where the concentration of plasma proteins in the plasma ultrafiltrate is sufficiently high. This balance is determined by the local ultrafiltration and resorption of plasma proteins and fluid. An increased ultrafiltration of plasma is caused by the breakdown of the normal barrier properties of the retinal vessels. This breakdown may be due to both structural changes in the capillary walls and an increase in the hydrostatic pressure of the vessels secondary to hyperperfusion. Breakdown of the blood-retina barrier can by studied by fluorescein angiography where intravenously injected fluorescein can be seen to leak out of the blood vessels, either corresponding to focal leakage points or more diffusely [18]. However, the fluorescein molecule is small, corresponding to about the size of a hydrated potassium ion, which implies that leakage of fluorescein does not necessarily reflect the presence of larger leakage points that would allow the leakage of plasma proteins [19].

It is a widely promulgated misconception that leakage of fluorescein per se reflects retinal oedema. Oedema is due to abnormal accumulation of fluid in the tissue because of a disturbance in the balance between hydrostatic, electric and osmotic forces across the vascular wall [20]. These variables are not fully described by studying the transport of fluorescein across the blood-retina barrier, and fluorescein leakage itself does not indicate that the retinal sensory function is disturbed [21]. Most of the variables involved in the formation of diabetic retinal oedema such as changes in the active transport of fluid over the retinal pigment epithelium and dynamic variations in the distribution of hard exudates, have only been sparsely studied. Therefore, fluorescein leakage is still a widely used marker

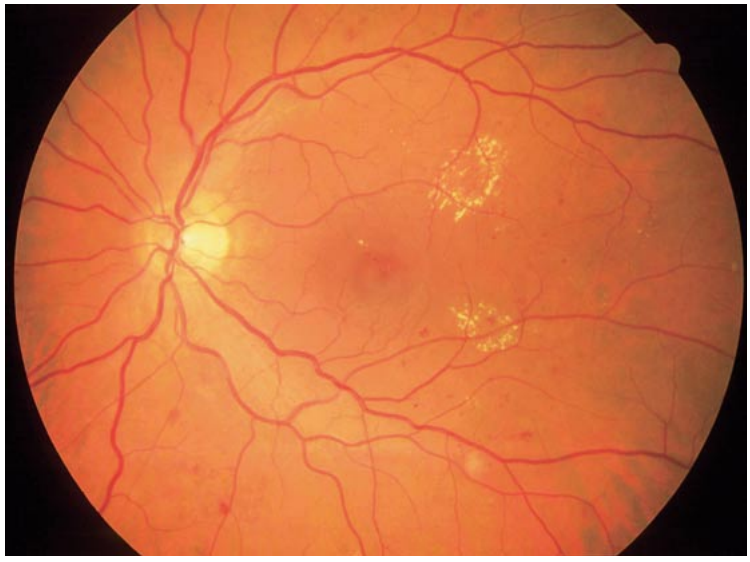

Fig. 5. Clinically significant macular oedema with hard exudates in the foveal region in addition to hard exudate rings.

of the mechanisms leading to diabetic retinal oedema.

Hard exudates develop later than microaneurysms and haemorrhages, but typically show the same spatial pattern of distribution with the lesions starting temporally from the fovea from where they may spread to other parts of the macular area. The density of hard exudates decreases from the vascular arcades and the lesion is typically absent from the retinal periphery. When exudate rings extend on each side of a temporal vascular arcade, the exudates located peripheral from the arcade will typically be much thinner than the segment located central from the arcade. In most cases, exudates are accompanied by retinal oedema which has a destructive effect on the neuronal tissue in the retina. Therefore, the presence of exudates and retinal oedema in the macular area is an indication that diabetic retinopathy has entered a potentially vision-threatening stage, so-called *diabetic maculopathy*. When an area with exudates and/or retinal oedema is either larger than one disk diameter and a part of this area is within one disk diameter from the fovea, or if these lesions develop within ½ disk diameter from the fovea, there is a high risk of visual damage, and the condition is termed *clinically significant macular oedema* (fig. 5). This advanced stage of diabetic maculopathy is treated with retinal photocoagulation which may halve the risk of developing visual loss [22]. Larger conglomerates of hard exudates that extend to the foveal area may block the light from reaching the photoreceptors and consequently induce visual loss and extrafoveal fixation. These visual disturbances may to some extent improve if retinal photocoagulation induces changes in retinal fluid dynamics so that the central exudates are resorbed [23]. However, visual impairment induced by retinal oedema will most often be irreversible. Retinal oedema is diagnosed semiquantitatively by binocular inspection [24] or quantitatively by optical coherence tomography scanning [25].

In younger diabetic patients, the initial sign of macular oedema may be reflections from the posterior hyaloid membrane in the macular area (fig. 6). These reflections are normal in younger persons because the light used to illuminate