Atypical cotton-wool spots

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Atypical cotton-wool spots in diabetic retinopathy differ from typical ones by their size, and because they comprise an extensive area of capillary closure. They thus resemble the atypical cotton-wool spots described by Wise, Dollery, and Henkind (1971). We have attempted to illustrate the circulatory conditions of the affected areas, comparing them with typical cotton-wool spots, as reported in the medical literature.

Material and methods

For this retrospective study we selected from our fluorescein angiographic material 4 cases of diabetic retinopathy which showed whitish-grey cotton-wool spots that exceeded $1\frac{1}{2}$ disc diameters. The quality and sequence of the pictures had to be such as to enable us to study the microcirculation in detail. The 4 cases chosen meet these criteria.

The recording of the fluorescein angiography was accomplished using a Zeiss fundus camera, and a blue exciting filter (Schott-GG 14.3) was incorporated; for the recording a Kodak Plus-X Pan 36 film was selected.

Results

The microvascular alterations in the area of the atypical cotton-wool spots will be discussed for each case separately.

CASE 1

A 70-year-old diabetic woman with normal blood pressure uses a daily regimen of 60 units of insulin lente. The lesion (Figs 1-3) is shown by a patch of white in the

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FIGS 1-3 *Fluorescein angiogram of 70-year-old diabetic. Atypical cotton-wool spot seen first before injection of dye, then 5 s after onset of arterial phase, and finally after an additional 3 s. A₁ represents first order arteriole, its origin being occluded. A₂ and V₃ share a common coarsened capillary network draining into V₄, and attempting to recanalize A₁. V₁ and V₂ contribute to filling of A₁*

centre which is gradually turning greyish towards its borders; it measures about $2\frac{1}{2}$ disc diameters, and lies within an area of capillary obliteration. Along its proximal border can be seen an arteriole which is completely occluded and is discernible only after dye enters the vessel retrogradely from neighbouring veins (V_1 and V_2). The distal portion of the occluded arteriole A_1 stains first, that is 6 seconds after onset of the arterial phase of the angiogram, and its total length is revealed after 5 additional seconds. Since no dye is entering the arteriole from the main arterial branch at its site of origin this presumably represents the point of initial obstruction.

The microcirculation surrounding the area of capillary obliteration displays various changes:

The venous branch (V_3) carries a reversed blood flow from the main venous trunk towards the lesion. It shows a common and coarsened capillary network with the upper branch of the arteriole A_2 . However, drainage of the total blood volume appears considerably impeded, partially emptying over a dilated capillary network into the venule V_4 . Another portion gradually approaches the occluded arteriole A_1 , only after having overcome a certain measure of resistance, and about 11 seconds after the appearance of the arterial phase of the angiogram it finally reaches the arteriole.

Most of the blood from the arteriole A_2 is drained to the venule V_4 via a coarsened capillary network. Thus an abnormal arterio-venous communication has established itself.

The occluded arteriole A_1 is retrogradely perfused with dye originating from the venules V_1 and V_2 .

CASE 2

A 61-year-old diabetic woman with normal blood pressure is being treated with a daily dose of 40 units of insulin lente. The lesion (Figs 4–5) displays a patch which appears to be white in the centre and greyish peripherally; its size is about 4 disc diameters. Total capillary obliteration extends over the whole area. The arterioles A_1 and A_2 particularly, but also the arteriole A_3 , are apparently responsible for the pathogenesis of this atypical cotton-wool lesion; they show a distinct narrowing of their lumina at their point of emergence from the main artery. Several branches of these arterioles that are directed towards the lesion are completely occluded.

Along the contour of the wide area of capillary obliteration, a garland of arterio-venous communications has established itself; this is composed of either a coarsened capillary network or single vascular channels on a pre-capillary level.

CASE 3

A 70-year-old diabetic woman is being treated with one anti-diabetic tablet daily. Her blood pressure is fluctuating between normal and hypertensive levels. The retinal lesion (Fig. 6) contains a patch, greyish-whitish in appearance and measuring about 2 disc diameters; no capillary structures are discernible within the lesion. The first order arterioles supplying the affected area is completely occluded; only a small stump at its origin can be seen. A broad arterio-venous communication transverses the upper corner of the lesion; this particular channel, as well as the two venous branches demarcating the area, displays aneurysms which are entirely orientated towards the lesion.

FIGS 4–5 Fluorescein angiogram of 61-year-old diabetic. Atypical cotton-wool spot seen at beginning of arterial phase, then 6 s thereafter. A_1 and A_2 represent first order arterioles displaying stenosis at their origin, their second order branches (arrow tip) directed towards lesion are occluded proximally, only a small stump remaining. A garland of arterio-venous communications (AV) straddles periphery of lesion

CASE 4

A 63-year-old diabetic woman with arterial hypertension is being treated by oral medication. The retinal lesion (Figs 7–8) is whitish-greyish in colour and measures slightly more than 2 disc diameters. The capillary network appears to be obliterated. The arteriole supplying the

FIG. 6 Fluorescein angiogram of 70-year-old diabetic. Atypical cotton-wool spot seen 4 s after onset of arterial phase. A minuscule stump of first order arteriole (A) is visible. AV represents an arterio-venous communication

affected area exhibits total obstruction at the point at which it emerges from the parent arterial branch. It is being perfused by dye retrogradely from the neighbouring arteriole A₂, and is finally recognizable in its total length 8 seconds after the onset of the arterial phase of the angiogram. It also displays considerable tortuosity, and many aneurysms are interspersed in its course. Broad collaterals exist not only to the neighbouring arteriole A₂, but also the venule V₁. The branches of the arteriole A₃ that are directed towards the lesion are also occluded; the proximal one remains partially patent and contributes to the retrograde filling of the occluded arteriole A₁.

A number of arterio-venous channels have developed. The connexion between A₂ and V₁ consists of a relatively broad vascular structure, and A₃ and A₄ are linked with V₂ and V₃ respectively through a distended capillary bed. The blood flow perfusing these arterio-venous communications appears to be accelerated.

Discussion and conclusions

Cotton-wool spots occur in a number of disease entities (for example, polyarteritis nodosa, systemic lupus erythematosus, subacute bacterial endocarditis, pernicious anaemia, etc.), but they are also a prominent feature in hypertensive and diabetic retinopathy. They appear as rounded, bright, milk-white, slightly raised spots with fluffy edges (Liebreich, 1859). They are usually located at the posterior pole, and rarely exceed 1/3 disc diameter (Williams, Drance, Harris, and Fairclough, 1971).

The pathomechanism of cotton-wool spots has been greatly elucidated by the study undertaken by Ashton and Harry (1963) who described these lesions as being whitish, measuring about 1/3 disc diameter,

FIGS 7-8 Fluorescein angiogram of 63-year-old diabetic. Atypical cotton-wool spot seen first before dye injection, then 10 s after onset of arterial phase. A₁ represents first order arteriole with occlusion at its origin. It is being filled retrogradely by A₂, and partially by A₃. Arterio-venous communications exist between A₂ and V₁, A₃ and V₂, A₄ and V₃. There appears to be an occlusion of first order arterioles of A₃ directed towards main lesion

lying superficially, and characterized mainly by a swelling of the nerve fibre layer. The swelling is supposedly the result of disturbed local circulation, but its basic mechanism could not be stated with certainty, and it was felt that a focal arteriolar spasm or a gradual narrowing of the supplying arteriole was responsible. The collapse of the capillary

circulation was considered to be due to two factors, a fall in the capillary pressure, and a rise of the surrounding tissue pressure. During the phase of resolution the local tissue swelling subsides, and the obliterated capillaries re-open.

Fluorescein angiography has contributed to the revelation of haemodynamic processes within the fundus. Dollery and Hodge (1963) stated that the predominant feature of soft exudates was the increased vascular permeability in the affected area, occasionally associated with point leakages from small arterioles. Gass (1968) also described the fluorescein angiographic appearance of cotton-wool spots in hypertensive retinopathy. Confirming the findings of a number of previous investigators, he described such a lesion as being nonfluorescent in the early angiogram, its margin being surrounded by dilated capillaries which contain microaneurysms. The cotton-wool spots supposedly represent areas where capillary perfusion is poor or absent and appear to result from a blockage of the flow near the origin of the first or second order arterioles, not caused by a sudden vascular obstruction, but rather by chronic arterial and arteriolar narrowing. He emphasized the smallness of the infarcted areas, which he attributed to the collateral channels which usually develop in their neighbourhood, and which in turn originate from adjacent arterioles. Gass (1970) mentioned also that cotton-wool spots in diabetics were indicative of arteriolar obstruction. Dollery, Henkind, Paterson, Ramalho, and Hill (1966), in their experimental work drew attention to the fact that collateral channels develop around the edges of the ischaemic infarcts. Kohner and Henkind (1970) commented on arterio-venous and veno-venous communications transverse areas of capillary closure and they stressed that both of these were not true shunt vessels in the sense of carrying rapid flow. Their work also confirmed that the nonperfused areas did contain a capillary network, although this was pathologically deranged, and not easily discernible by fluorescein angiography.

Wise and others (1971) distinguished between typical and atypical cotton-wool spots, the latter being of a light grey colour indicating a patch of local capillary obstruction. The size of the area involved appears to be considerably larger than with typical cotton-wool spots. However, unlike the latter, atypical cotton-wool spots occur frequently in diabetics without being associated with hypertension. The lesions described share certain similarities with the atypical cotton-wool spots as outlined above. They are either of a greyish colour or they contain a whitish area which is gradually turning greyish at the edges. They are also mainly composed of a capillary-free area, and their size is considerably larger than the typical cotton-wool spot ranging between about 2 and 4 disc diameters.

One or more arterioles supplying the affected area can be responsible for the development of such a lesion. The extent of the lesion corresponds with the calibre and size of the occluded arteriole. The site of occlusion appears to be confined to the point at which the arteriole emerges from the main arterial branch; the narrowing of the entire length of an arteriole does not appear to be the aetiological trigger mechanism; this is shown by the fact that only a remaining minuscule stump of the occluded arteriole is discernible, or that it can be seen only by retrograde filling without the slightest stain originating from the main arterial branch. The obstruction may be either total (Cases 1, 3, and 4), or (Case 2) a focal narrowing at the site of origin of the first order arteriole followed by total occlusion of the second order arteriole. Second order arterioles which extend into the affected area may also be obstructed on a secondary basis, without their parent first order arteriole being affected.

Once the arterial supply of a relatively large retinal area has become obstructed, an attempt is made to restore the flow in the nonperfused capillary network. This is accomplished by extensions of adjacent arterioles and by neighbouring venules carrying a reversed blood flow.

It is of interest to note that despite the efforts to restore the flow, the capillary net will fill only after considerable delay, thus apparently confirming the concept that tissue swelling in this area exerts considerable pressure upon the capillaries. During such a process of recanalization, an arteriole and a venule (the latter carrying a reversed flow) may share a common capillary net resulting in a considerable stagnation of blood circulation, and finally leading to dilatation and alteration of the affected capillaries. A site of drainage will then have to be developed, which may be accomplished over another coarsened capillary net that will have to carry a blood volume in excess of the normal, finally reaching its recipient venule. One may therefore conclude that coarsening of the capillaries around the edges of the infarcted areas is not only the result of tissue hypoxia, but more significantly can have developed mechanically.

Arterio-venous communications are a prominent feature within the compounds of atypical cotton-wool patches. One type of arterio-venous communication is characteristic as it follows closely the perimeter of the avascular area either as a coarsened precapillary network, or as a small singular vessel linking the artery and the vein. Since its location is clearly not on a random basis, it must be assumed that it aids the drainage of the arterial influx, thus serving a haemodynamic necessity. The blood flow in these arterio-venous communications appears to be either of normal velocity or is accelerated; however, if the blood flow is accelerated this does not in itself imply a causative relationship to the aetiology of atypical

cotton-wool patches. Since collateral channels are such a distinctive feature of large (atypical) cotton-wool patches, the supposition that typical cotton-wool spots are small because of the occurrence of such vascular interconnexions (Gass, 1970) does not seem to be valid.

Veins or venous branches located at the edge of a nonperfused area may display secondary changes, such as, staining of their wall, and the formation of aneurysms characteristically orientated towards the lesion, suggesting that these alterations are of secondary nature.

Summary

Atypical cotton-wool spots in four selected cases of diabetic retinopathy are discussed. The most striking

characteristic distinguishing them from typical cotton-wool spots is their size, which ranges from about 2 to 4 disc diameters. They develop after stenosis or a complete obstruction of a first order arteriole at the point at which it emerges from the parent arterial branch. The size of the lesion corresponds with the size of the affected arteriole. Restoration of local circulation is attempted by neighbouring arterioles and venules, the latter carrying a reversed blood flow. Arterio-venous communications along the border of the infarcted area are a prominent feature, most likely attributable to the necessity of free drainage of the arterial influx. The same haemodynamic principle applies to the coarsening of the adjacent capillary bed. Secondary changes of the bordering venous branches include aneurysm formation and the staining of the venous wall.

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