Retinal cotton-wool spots: an early finding in diabetic retinopathy?

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SUMMARY Five insulin dependent diabetic patients are reported on who had a few small retinal cotton-wool spots or 'soft exudates' either totally isolated or associated with fewer than 10 microaneurysms. These observations suggest that cotton-wool spots may be an early finding in diabetic retinopathy. Significant biological abnormalities in these patients were high levels of glycosylated haemoglobin and mild increases in thrombin generation, indicating slight activation of the coagulation system. The possible significance of these clinical and biological findings is discussed.

A prime aetiological agent in diabetic retinopathy would appear to be chronic hyperglycaemia and the associated metabolic changes of diabetes mellitus.¹ However, the precise causes of both the onset and the development of the characteristic retinal changes seen in diabetic patients are poorly understood. Efforts are increasingly being directed at studying the early stages of diabetic retinopathy in an attempt to find a clue to its pathogenesis.

Microaneurysms and deep punctate haemorrhages appearing first in the posterior retina, particularly temporal to the macula, are usually regarded as the earliest clinical manifestation of diabetic retinopathy.^{2,3} This observation has been made in ophthalmoscope and fundus photograph studies of the natural history of the retinopathy found in diabetic patients.^{2,3} More recently studies in patients with no clinical evidence of diabetic retinopathy, and by means of refined clinical techniques such as fluorescein angiography^{4,5} and vitreous fluorophotometry,^{6,7} have shown that leakage of fluorescein from the retinal vessels or the retinal pigment epithelium may precede the development of retinal microaneurysms. However, this finding remains disputed because it has not been confirmed by other investigators.⁸⁻¹²

In pathology specimens of diabetic patients retinal capillaries show a definite early loss of intramural pericytes as well as the presence of microaneurysms.^{13,14} Microaneurysms and pericyte loss may either be present together or occur in separate

areas of the retinal capillary bed. The exact time sequence of these two changes is unknown. As retinopathy worsens in diabetic patients there is an increasing number of totally acellular capillaries which no longer carry blood.¹⁵ It has been suggested that, if complete occlusion of a precapillary arteriole in the superficial layers of the retina occurs suddenly, a cotton-wool spot is seen on clinical examination of the retina.¹⁶⁻¹⁸ However, cotton-wool spots are usually described as part of the advanced preproliferative stage of diabetic retinopathy and where the retinal capillary bed already shows marked abnormalities.^{3,17} They may also be seen transiently following improved diabetic control.^{19,22} In diabetic patients the exact pathogenesis of these cotton-wool spots remains unclear.²³

We have had the opportunity to examine five insulin dependent diabetic patients in whom small cotton-wool spots, supposedly superficial retinal microinfarcts, were seen in the retina either as the sole diabetic lesion or in association with only a few microaneurysms. Thus, the purpose of this paper is to describe the retinal findings that we observed in these diabetic patients and to discuss their possible significance for the pathogenesis of diabetic retinopathy.

Material and methods

All five insulin dependent diabetic patients were examined at the National Eye Institute (NEI) in Bethesda, Maryland. Ocular examination included best visual acuity, Amsler grid testing, slit-lamp

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examination, and dilated fundus examination, with contact lens examination of the retina. Seven standard photographic fields of the retina, as defined by the Diabetic Retinopathy Study (DRS),²⁴ were obtained. In three patients (1 to 3) fluorescein angiography of the macula, the area temporal to the macula, and of any field where microaneurysms had been seen on fundus examination was performed in both eyes. Colour vision was assessed by Lanthony desaturated D-15,²⁵ 100-hue, and chromagraph²⁶ tests. Contrast sensitivity was also performed in patient 1 by the procedure described by Higgins *et al.*²⁷

In all five patients a detailed medical history and a physical examination, including blood pressure and neurological examination, were performed. In all five patients levels of glycosylated haemoglobin were determined by ion-exchange chromatography. In four patients blood was also collected for coagulation studies, without stasis, from an antecubital vein. Routine coagulation screening included a pro-thrombin time, partial thromboplastin time, thrombin time, and plasma fibrinogen levels.²⁸ Plasma levels of factor VIII/von Willebrand factor were assessed by a one-stage VIII:C assay, a Laurell assay for VIII-related antigen (VIIR:Ag), ristocetin cofactor activity assay,²⁹ and agarose electrophoresis for visualisation of VIIR:Ag multimers.³⁰ Plasma levels of fibrinopeptide A (FPA) were measured by a radioimmunoassay (Mallinkrodt, St Louis, MO) and plasma levels of β thromboglobulin (β TG) and platelet factor 4 (PF4) by radioimmunoassays (Amersham, Arlington Heights, IL and Abbott, North Chicago, IL, respectively). Platelet size was determined with a Particle Data Cellozone computerised system.³¹ Patients 1 and 2 were seen on a second occasion one year after the first examination, and at that time coagulation studies on them were repeated. We chose not to perform platelet aggregation studies because this in-vitro phenomenon is probably not a quantitatively sensitive method for evaluating platelet activation and is subject to significant technical problems.

In all five patients kidney function was also assessed. Serum blood urea nitrogen (BUN) and creatinine, creatinine clearance, and 24-hour urine collection for 24-hour protein excretion determination were studied. Nerve conduction studies in the right median motor and sensory nerves and peroneal motor nerve were performed in patients 1 and 3.

Case reports

PATIENT 1

This was a 20-year-old white man whose insulin dependent diabetes was diagnosed at 13 years of age.

Fig. 1A

Fig. 1B

Fig. 1 Patient 1, right eye. A: Three cotton-wool spots in the macular area (arrows). B: fluorescein angiogram showing hypofluorescence in the same locations and two microaneurysms at the posterior pole.

He received two injections of regular and NPH insulin a day (64 units). He had never had a diabetic coma but had rare episodes of mild hypoglycaemia; he tested his blood for glucose levels once a day. There was no family history of diabetes. Ocular examination was normal except for the right retina, which showed five microaneurysms and four small, elongated superficial grey-white cotton-wool spots in the superior and inferior parts of the macula. These were very prominent on biomicroscopy and fundus photography and corresponded to areas of hypo-

Fig. 2A

Fig. 2B

Fig. 2 Patient 1, left eye. A: Two isolated cotton-wool spots in the macular area (arrows). B: Fluorescein angiogram showing hypofluorescence in the same locations and no other diabetic retinal abnormality.

fluorescence without abnormalities of the surrounding capillary bed on fluorescein angiography (Figs. 1A, 1B). In the left eye there were two similar cotton-wool spots in the macular area and no other diabetic lesion (Figs. 2A, 2B).

In each eye central retinal artery diastolic pressure was 39 mmHg. Colour vision tests were normal. Contrast sensitivity studies showed no abnormality in comparison with age matched controls.²⁷

The patient had no clinical evidence of diabetic neuropathy but had slower motor nerve conduction velocity (N) in the right median motor (N=49 m/s)

Fig. 3 Patient 2, left eye. One small cotton-wool spot (arrow) in field 7 of the DRS photographs.

and peroneal motor (N=31 m/s) nerves. Standing diastolic blood pressure was 150/88 mmHg. Physical examination was on two occasions normal, as was kidney function. The level of glycosylated haemoglobin was high (13.5%). On two occasions he had a raised plasma fibrinopeptide A (FPA) level and on one occasion a minimal elevation of β thromboglobulin (β TG) and platelet factor 4 (PF4) (Table 1).

At follow-up one and half years later fundus examination revealed in the right eye five microaneurysms and one remaining cotton-wool spot in the macula. In the macula of the left eye there was only one small cotton-wool spot.

PATIENT 2

This was a 33-year-old white man who had had diabetes for four years. There was a family history of diabetes in a great-great-grandmother. He received one injection of 32 units of insulin lente a day. He did not test his urine or blood regularly and had a relatively poor metabolic control, as reflected by the levels of glycosylated haemoglobin (14.4% of normal haemoglobin). Ocular examination was normal except for the left retina, which showed microaneurysms—two at the posterior pole and one along the inferior temporal retinal vein—and in field 7 of the DRS photographs one 100 μ m, white, well defined, isolated, rounded cotton-wool spot (Fig. 3). Colour vision was normal.

Physical examination showed nothing abnormal. Blood pressure was normal, 120/72 mmHg in the supine and 132/84 mmHg in the standing position.

Table 1 Blood coagulation and platelet studies in four insulin dependent diabetic patients with retinal cotton-wool spots

	FPA ng/ml	Factor VIII/von Willebrand factor (vW)				β TG ng/ml	PF4 ng/ml	Platelet size μm^3
		VIII:C	Ristocetin cofactor	VIII R:Ag	vW multimers			
Case 1								
Measurement								
A*	9.6	144%	180%	193%	Normal	53.4	10.1	—
B**	3.4	123%	126%	130%	Normal	33.4	5.1	—
Case 2								
A	0.8	77%	103%	135%	Normal	42.6	9.8	6.87
B	2.3	93%	102%	148%	Normal	33.3	5.3	—
Case 3	2.8	75%	91%	90%	Normal	30.5	4.4	7.28
Case 5	3.6	96%	128%	108%	Normal	37.9	4.8	7.28
Normal range†	(0.5–1.3)	(50–150%)	(50–160%)	(58–160%)	‡	(10.6–41.4)	(1.9–10.0)	(4.1–9.0)

FPA=fibrinopeptide A. VIII:C=factor VIII: C activity. VIII R:Ag=factor VIII related antigen. β TG= β thromboglobulin. PF4=platelet factor 4.

†As obtained from a group of 24 normal persons not on medication, age 20–50, with no history of bleeding disorder.

A* results of the first and B** second measurement of these coagulation factors.

‡All multimers visualised and no anomalous bands or abnormally high molecular weight bands seen.

There was no evidence of peripheral diabetic neuropathy. Incomplete bladder emptying suggested some autonomic neuropathy. Kidney function was normal. Coagulation studies showed a slight elevation of fibrinopeptide A (FPA) on one occasion only (Table 1).

One year later the retinal findings were similar except in the left eye, where one flame shaped haemorrhage lay close to the cotton-wool spot which was still present.

PATIENT 3

This was a 25-year-old white woman who was diagnosed as diabetic at 18 years of age. She received one injection of insulin per day, 11 units of regular and 26 units of NPH. She had had one hypoglycaemic coma. She tested her blood for glucose levels twice a day. There was a family history of type II diabetes in a paternal grandmother. Ocular examination was normal except for the retina of the right eye, where there were 10 microaneurysms and one small, grey-white, elongated superficial cotton-wool spot above the macula, and in the left eye where there were six microaneurysms but no other diabetic retinal lesion (Fig. 4). In the right eye colour vision tests showed a mild blue-yellow defect on FM 100 hue and D-15 desaturated tests. Colour vision was normal in the left eye.

Her blood pressure was normal, 104/68 mmHg supine, 98/60 mmHg sitting. The patient had no clinical evidence of diabetic neuropathy, though nerve conduction velocity (N) of the motor peroneal nerve was decreased (N=41 m/s). Kidney function was normal. Glycosylated haemoglobin was raised to 12.7% of normal haemoglobin. Coagulation studies showed slightly increased FPA on the one occasion

when it was measured; other coagulation and platelet studies were normal (Table 1).

One year follow-up showed that in the right eye the small cotton-wool spot was still present, and five of the microaneurysms, initially seen close to the fovea, were no longer visible. In the left eye there were nine microaneurysms.

PATIENT 4

This was a 46-year-old white woman who had received insulin therapy for 10 years, one insulin injection of 30 units of lente insulin a day. Examination of visual acuity and anterior segment gave normal results. In the right eye there were three

Fig. 4 Patient 3, right eye. One cotton-wool spot (arrow) above the macula with microaneurysms.

Fig. 5 Patient 4, right eye. One cotton-wool spot (arrow) along the inferior nasal artery, associated with one microaneurysm.

microaneurysms at the posterior pole. Almost a disc diameter from the optic disc there was also a small greyish elongated cotton-wool spot along the inferior nasal artery, associated with one microaneurysm (Fig. 5). In the left eye there was only one microaneurysm, inferior to the fovea.

Blood pressure was normal, 124/84 mmHg supine and 118/80 mmHg standing. Physical examination showed nothing abnormal. The patient had

Fig. 6 Patient 5, right eye. One small cotton-wool spot (arrow) along the inferior temporal vessels. No other diabetic retinal lesion in either eye.

decreased triceps and quadriceps reflexes. Serum BUN and creatinine were normal. Glycosylated haemoglobin was 11.3% of normal haemoglobin. Coagulation studies were not available.

PATIENT 5

This was a 34-year-old white man whose diabetes was diagnosed at 31 years of age. He received two injections of 10 units of insulin NPH a day and he tested his blood sugar three times a week. There was a family history of type II diabetes in an uncle. Ocular examination was normal except for one small, superficial grey-white, rounded cotton-wool spot along the inferior temporal retinal vessels in the right eye, which had been noted one year before (Fig. 6). Blood pressure was 102/78 mmHg standing and 100/70 mmHg supine. There was no clinical evidence of diabetic neuropathy. Kidney function was normal. Glycosylated haemoglobin was 7.8% of normal haemoglobin. Coagulation studies showed a slight increase in FPA without other abnormalities (Table 1).

Discussion

We report on five young insulin dependent diabetic patients who had small retinal cotton-wool spots or 'soft exudates,' either isolated or associated with only a few microaneurysms elsewhere in the fundus. Independent confirmation of these retinal findings came from the Fundus Photography Reading Center in Madison, where the fundus photographs of patients 1, 2, and 4 had been subsequently reviewed for a separate study.

These cotton-wool spots, though smaller, had a similar appearance to those previously described in diabetic patients,^{3 17-19 21 22 31 32} where they were usually seen along the upper and lower arcades of the optic nerve fibres, and also at the border of the disc and out for at least four disc diameters. In two of our diabetic patients, however, the cotton-wool spots were in the macula itself, in the space between adjacent vessels, and this location may have explained their somewhat linear configuration.

Esmann *et al.*³² have previously noted that cotton-wool spots in the absence of systemic hypertension or renal disease are quite a frequent finding in diabetic retinopathy. In none of our patients was the blood pressure raised either at the initial or at the follow-up examination, and none had any renal abnormality. While in diabetic patients 'soft exudates' may also occur in the mid retinal capillary bed, where they are seen as an area of greying and initially somewhat thickened retina, those occurring in the superficial retinal layers are more easily noticeable. However, these 'soft exudates' may still be easily overlooked by

direct ophthalmoscopy, particularly in the macular area of young patients whose retinal reflexes are prominent, and they may be clearly identified only on careful biomicroscopic examination of the retina, as was performed in the present study.

In diabetic patients the appearance of numerous cotton-wool spots is usually indicative of rapidly advancing retinopathy.³ In our patients, however, there were only a few small cotton-wool spots and no adjacent capillary abnormalities, venous dilatation, retinal haemorrhages, oedema or exudates, or intra-retinal microvascular abnormalities (IRMA) to suggest preproliferative diabetic retinopathy.³ In two eyes the cotton-wool spots were the only diabetic retinal findings. Furthermore in the three patients who were seen at least one year later these soft exudates were still present, while the diabetic retinopathy had not otherwise worsened. In diabetic patients under 40 years of age the mean half life of the cotton-wool spot has been found to be as long as 8-1 months.¹⁷

Improved metabolic control in diabetic patients with mild to moderate diabetic retinopathy at baseline may also evoke cotton-wool spots and sometimes IRMA, but these lesions appear to be transient and are not followed by the development of proliferative diabetic retinopathy in these patients.^{20,22} None of our patients had made any significant change in their insulin regimen during the previous 12 months. Thus cotton-wool spots in different clinical situations may have a different prognostic value and their causes may well differ.

The histological features of the cotton-wool spots that we observed are those of an area of swelling of the nerve fibre layer with cytooid bodies.¹⁶ In diabetic patients the retinal capillaries on trypsin digest preparation of that same area are thin and show hypostaining and loss of nuclei, particularly of mural cells.¹⁶ It has been postulated that cotton-wool spots in diabetes are due to acute focal ischaemia. Ashton¹³ has described marked narrowing of the lumen of the precapillary arteriole as a cause of capillary dropout. The reason that narrowing occurs there is not clear. Furthermore this narrowing was described in cases of advanced diabetic retinopathy and might be the result rather than the cause of the collapse of the capillary bed. It remains contentious whether it is microinfarction which is responsible for soft exudates or whether the localised area of capillary closure is a consequence of the local tissue swelling.^{23,33}

Whether retinal lesions in diabetic patients are due to a local metabolic disturbance, such as hyperglycaemia with resulting increase in the sorbitol pathway,³⁴ or to alteration in blood flow secondary to increased blood viscosity,³⁵⁻³⁷ or to local hypoxia,³⁸ is not clear. It is noteworthy that in four of the five

patients in the present study the control of their diabetes at the time of examination was relatively poor, as reflected by high levels of glycosylated haemoglobin.

Activation of coagulation factors and platelets has also been implicated in the pathogenesis of vascular lesions in diabetic patients.³⁹⁻⁴⁴ We observed a slight increase of plasma fibrinopeptide A in three of the four patients that we tested. In the coagulation cascade fibrinopeptide A is specifically cleaved from the A α -chain of fibrinogen by thrombin. Therefore our results suggest a rather mild increase in thrombin generation in vivo. The lack of increase in the platelet derived proteins (β TG and PF4), as well as normal levels (with one exception) of factor VIII/von Willebrand factor (vWf), indicate no significant platelet activation or endothelial cell release of vWf in the diabetic patients reported on here. No absolute causal relationship between the observed thrombin formation in vivo and the cotton-wool spots can be defined. It does appear, however, that activation of platelets is very unlikely to have played any significant part at this stage in the retinopathy of our diabetic patients.

In summary, we found that five insulin dependent diabetic patients had small retinal cotton-wool spots, either totally isolated or associated with less than 10 microaneurysms, while having no other diabetic retinal lesion. From our observation one might speculate that cotton-wool spots may be regarded as an early change of diabetic retinopathy. Poor metabolic control of the diabetes and mild increases in thrombin generation, suggesting activation of the blood coagulation factors, were the only significant biological abnormalities associated with the retinal lesions in these patients. These findings deserve further investigation for their possible significance in the pathogenesis of diabetic retinopathy.

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