

Review

THE MYSTERY OF COTTON-WOOL SPOTS A REVIEW OF RECENT AND HISTORICAL DESCRIPTIONS

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Abstract

Purpose: Cotton-wool spots (CWSs) lie superficially as opaque swellings in the retina, with occurring as acute lesions. The occurrence of CWSs is a sign of serious vascular damage.

Methods: CWSs can usually be diagnosed by ophthalmoscopy. In the literature, there are reports of examinations by fluorescein angiography, visual fields, or optical coherence tomography (OCT).

Results: CWSs are non-specific, as they can occur in different diseases involving the retinal vascular system. CWSs are localized accumulations of axoplasmic debris within adjacent bundles of ganglion cell axons. They occur after arteriolar occlusion at the borders of large ischemic areas, and should not be regarded as retinal fiber layer infarcts (McLeod). The "principal constituent of the CWS" are cytooid bodies. Microaneurysms may be present at the edge of some CWSs in different diseases with retinal ischemia. The presence of many CWSs may be a significant predictor for the development of rubeosis iridis, for instance in a patient with central retinal vein occlusion. CWSs have disappeared in weeks or occasionally a few months in hypertensive patients. However, in diabetic patients, they may persist for as long as one or two years.

CWSs have been the most frequent ocular findings in patients with Aids.

Aids patients show a strong correlation between CWSs and multiple opportunistic infections. Aids patients with CWSs have shown a poorer prognosis compared to those without CWSs. Leukocyte counts were found to be significantly lower, and the proportion of patients with significant weight loss was greater among Aids patients who revealed CWSs.

Conclusion: CWSs delineate ischemic retina, which is attributed to obstruction of axoplasmic transport. Ischemia is the essential factor in the development of CWSs. Early detection of a CWS is necessary to evaluate a hitherto occult systemic disease with a vascular component.

INTRODUCTION

A cotton-wool spot (CWS) usually occurs as an asymptomatic retinal sign. Only rarely, a patient may notice blurred vision in conjunction with the occurrence of CWS, or CWSs may appear together with an

amaurosis fugax attack. Therefore, every patient who notices floaters or a brief visual disturbance, possibly a significant predictor of disease, should be examined ophthalmoscopically.

The detection of CWSs at an early stage is necessary, because they could be the first sign of a systemic disease. Even an isolated CWS should alert a clinician to arrange an extensive examination of the patient. The occurrence of CWSs is usually a serious sign of vascular damage (Andersen, 1978) [1].

I. DEFINITION OF COTTON-WOOL SPOTS

There are several terms in the literature for "cotton-wool spots" (CWSs) or "cotton-wool patches", such as "snow bank lesions" or "soft exudates". The latter is a misnomer as the patches are not exudates. They appear as whitish-grey, fluffy deposits with frayed edges, as if they had been "pulled from a roll of cotton" (Matas 1977) [192]. They lie superficially as opaque swellings in the retina; most occur as acute lesions.

II. PATHOPHYSIOLOGY

1. PHYSIOLOGY OF AXOPLASMIC TRANSPORT AND ITS DISTURBANCE

A constant flow of subcellular particles and molecules has been identified within ganglion-cell axons of nerve-cells, the "axoplasmic transport". This transport has been investigated with enzyme markers and autoradiography. Mitochondria, secretory vesicles, enzymes, and ribonucleic acid are among the conducted cellular constituents of axoplasm. The axonal transport is bidirectional. Slow and rapid phases of axoplasmic flow have been distinguished (Kirkpatrick & Stern 1973) [147]. CWSs should be regarded as localised accumulations of axoplasmic debris in the retinal nerve-fiber layer. Slow and rapid phases of axoplasmic flow have been distinguished in retinal ganglion-cell axons. Retrograde axonal flow has been demonstrated between synaptic terminals in the lateral geniculate body and the inner retina. Orthograde and retrograde axoplasmic transport in retinal ganglion-cell axons can be interrupted by axonal ischemia (McLeod 1975) [199].

Quigley & Anderson (1976) [252] reported that orthograde transport depends on oxygen, ATP energy, and temperature. Ischemia or mechanical pressure can interrupt the axoplasmic transport. When intraocular pressure has experimentally raised to 30 mm Hg below

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mean arterial blood pressure in animals, transport blockage was detected within two hours.

CWS reflects obstruction of axoplasmic flow

Duke-Elder (1967) [72] assumed that localised destruction of several axons, as may be caused by a retinal infarct with interruption by anoxia, may cause CWSs. The common factor would be ischemia and anoxia due to acute occlusion of a focal area of small vessels. Local factors were enumerated such as an infarct, thrombus, micro-embolism or spasm, or a sudden decrease in retinal arteriolar pressure. However, McLeod (1976a) [200] explained the pathophysiology of CWSs in greater detail. He emphasized that CWSs represent the amount of axoplasmic debris. CWSs reflect obstruction of orthograde or retrograde axoplasmic transport in the unmyelinated axons. Orthograde and retrograde axoplasmic flow occur simultaneously, but independently. CWSs occur after arteriolar occlusion at the borders of large ischemic areas. They often define the borders of large ischemic areas, but do not represent the full extent of the ischemic retinal area, for instance after an arteriolar occlusion. Their size depends largely on the number of affected axons. They are thus most dense in the temporal peripapillary region (McLeod, 1976b) [201].

Experiments in pigs were carried out with argon laser photocoagulation of the retina to occlude small retinal arterioles. McLeod et al. (1977) [202] observed ischemic necrosis of the inner retina. Swollen axon terminals were packed with cytoplasmic organelles in the retinal nerve-fiber layer on the infarct's peripheral border. CWSs should be regarded as localised accumulations of axoplasmic debris in the retinal nerve-fiber layer.

Experiments in monkeys by Kishi et al. (1985) [148] showed that peripapillary CWSs occurred as a result of accumulation of axoplasmic components due to the blockage of orthograde axonal transport within the ischemic optic disc. Multifocal ischemia causes a spotty accumulation of axoplasmic organelles.

Graham (1990) [101] reported that CWSs indicate blockage of a retinal arteriole, caused by abnormalities in the vascular endothelium, blockage by abnormal erythrocytes, or emboli. The CWS is produced by occlusion of the precapillary arterioles and reflects the breakdown of retrograde and orthograde axoplasmic flow. The axoplasmic debris accumulates at the junction of healthy and anoxic retina. Folberg & Bernardino (1998) [83] stressed that CWSs result from ischemia-induced transection of the axons. Axoplasmic transport accumulates at the zone of transection in bulbous microscopic swellings that were called "cytoid" (cell-like) bodies.

McLeod (2005) [207] emphasized that CWSs are localised accumulations of axoplasmic debris within adjacent bundles of ganglion cell axons. Their formation is widely held to reflect focal ischemia from terminal arteriolar occlusion, but credible evidence supporting this view is lacking.

McLeod (2005) [207] also conceded "while unproved, the possibility remains that CWSs sometimes reflect occlusions of the smallest (terminal) retinal arterioles. However, this mechanism has no more basis in theory than several other mechanisms, and then

only in the context of a restricted collateral microcirculation." CWSs are nothing more than "sentinels" of retinal nerve-fiber, and should not be regarded as retinal fiber layer infarcts [207].

Jampol & Rabb (1981) [133] pointed out that the non-perfused areas often correspond to obstructed precapillary arterioles. With inner retinal ischemia there was orthograde or retrograde axoplasmic stasis or both, with an accumulation of cytoplasmic debris in the nerve-fiber layer.

2. TRACER STUDIES

McEwen & Grafstein (1968) [197] administered labeled leucine into the eye of a goldfish and found that radioactive protein rapidly accumulated in the collateral optic tectum. In the transported protein, the label remained attached to leucine. This material reached the tectum six to 12 hours after the isotope injection, revealing a rate of transport of at least 40 mm per day. McLeod et al. (1977) [202] studied amino-acid uptake and transport in retinal ganglion cells by autoradiography following an intravitreal injection of [³H] leucine in animals. When leucine was injected at the same time as retinal laser coagulation with arteriolar occlusion, on the peripheral side of two-day-old infarcts, label became concentrated in the swollen axon-terminals. However, on the disc side of infarcts, label was absent from the terminal. The accumulation of [³H] leucine and organelles was attributed to interruption of orthograde axoplasmic transport.

In an additional experiment, [³H] leucine was injected into the vitreous two days prior to laser coagulation. Conspicuously, label became distributed throughout the axoplasm, and then accumulated in swollen axon terminals on both sides of infarcts. This observation showed that both orthograde and retrograde axoplasmic flow were obstructed. Minckler & Bunt (1977) [213] injected radioisotopes into the vitreous of eyes with marked papilledema in seven monkeys with ocular hypotony. Orthograde axoplasmic transport was blocked in swollen axons of the optic disc, shown by autoradiography. Retrograde transport was studied in the same eyes by horseradish peroxidase injection into the dorsal lateral geniculate nuclei or optic tracts. The authors emphasized that axoplasmic transport in the optic nerve head is sensitive to alterations in intraocular pressure. Tsukada & Chihara (1986) [326] labeled proteins in retinal ganglion cells with [³⁵S] methionine and [³H] leucine. The components of fast, axonally-transported protein were studied in 20 nerves of rabbits. In diabetic animals, the axonal transported radioactivity was one-fifth that of the normal control animals.

3. VELOCITY AND TRANSPORTED CONTENT OF AXOPLASM

Weiss & Hiscoe (1948) [338] found that the rate of interaxonal flow was about 25 times faster than that of the "intra-axonal convection" (cca. 1 mm per hour against cca. 1 mm per day). Lubinska (1964) examined the acetylcholine esterase (AChE) transport velocity and found 30-70 mm a day in warm-blooded animals.

Lubinska (1964) [182] suggested that a continual migration of the neuronal cytoplasm from the perikaryon to the nerve endings exists and from there back to the perikaryon. It was suggested that streaming in the axons is bidirectional, with some axoplasmic layers moving in the cellulifugal and other cellulipetal direction.

Lubinska & Niemierko (1971) [183] examined the amount of enzyme accumulating near the cut ends under various experimental conditions. The velocity of the axonal transport of acetylcholinesterase (ACHE) was 260 mm/day in the proximo-distal, and 134 mm/day in the disto-proximal direction. McEwen & Grafstein (1968) [197] found that the slow component moves at a rate of 0.4 mm per day, while the fast component moves about 100 times as fast. The slowly-moving component contains about 5 times as much radioactivity as the fast component. In the slowly-moving component, 60% particulate matter and 40% soluble protein were detected. Tso et al. (1988) [324] observed focal capillary leakage prior to CWSs development. They also mentioned that CWSs are an accumulation of axoplasmic components in the nerve-fiber layer consisting of mitochondria, lamellated dense bodies, and axoplasmic ground substance in the proximal or distal end of axons in the ischemic area.

Axoplasmic flow rate of the slow component in monkeys after intraocular injections of [³H] leucine was estimated as approximately 1 mm per day and that of the fast component in the range of 100 mm per day (Chou 1970) [53].

The labeled activity moving down the nerve was determined to be 415 mm/day when corrected for temperature. The same rate was found, regardless of the size of nerve taken, in different animals as well. Age did not seem to affect the rate either. Retrograde transport is estimated to travel at 130 to 220 mm per day (Ochs 1974) [226].

Quigley & Anderson (1976) [252] reported that orthograde transport carries microsomal material at 400 mm per day (rapid phase), whereas slower phases consisting of soluble protein and mitochondria move at 1 to 3 mm per day.

The inception of a CWS

Brown et al. (1985) [39] pointed out that CWSs were induced by an obstruction of a retinal arteriole in many vascular diseases or in experimental embolization with minute glass spheres.

4. EXPERIMENTS

Occlusion of retinal arterioles with glass ballotini

Ashton & Henkind (1965) [13] studied feline retinal edema in the region of the arteriolar occlusion approximately three to 24 hours after injection with ballotini (lead glass spheres ranging in diameter from approximately 15 to 75 μ). Some of the smaller patches of edema closely resembled CWSs and in one specimen "Cajal-type" nerve-fiber swelling was observed.

In animal experiments with glass microspheres (ranging between 15 to 40 μ in size), injected into the carotid artery of pigs, Shakib & Ashton (1966) [295] observed white patches in the retina resembling CWSs in humans between one and four days after emboliza-

tion. Intracellular swelling had developed 30-40 minutes after embolization as a greyish-white discoloration, initially not characteristic of a CWS. However, 24 hours later, when intracytoplasmic proliferation occurred in addition to the swelling, the typical appearance developed. The CWS represented a focal reaction on the part of injured axons. By seven days after embolization, the CWSs had largely faded. Studies four to six weeks later revealed an almost normal retina.

Electron-microscopy revealed that the white fluffy appearance of the CWS was primarily due to intracellular swelling in the structures of the inner retinal layers which is why the experimental lesion resembled occluded arteries, as in arterial hypertension. Thus, a common pathogenesis of different diseases was postulated, meaning that ischemia due to arterial occlusion is the essential factor in the development of CWSs. Ashton (1972) [16] again demonstrated that CWSs occurred in the vicinity of occlusion of terminal arterioles in experimental embolization studies by introducing glass microspheres into the carotid circulation. Within one hour after embolization, focal swelling with inner retina opacification in the embolized area was observed. A subsequent massive fusiform swelling of the nerve-fibers was found. Striking histological changes were observed five to 72 hours later, in the swollen segments of nerve-fibers: mitochondria, membrane-bound microvesicles, dense bodies, membranous whorls, and neurofilaments had filled the distended nerve-fiber segments. Ashton (1972) [16] also found that degenerative changes in axons resulted in the formation of cytooid bodies. The patent capillaries at the margin of the lesion occasionally showed aneurysmal dilatations.

Experiments with latex microspheres

Gay et al. (1964) [92] used latex microspheres to create occlusions in the chorioretinal vasculature of the canine eye, observing capillary occlusion in the nerve-fiber layer; cytooid bodies were noted two days after injection. Multiple capillaries, occluded by spheres, were observed adjacent to the cytooid body lesions. Retinal ischemia beneath the cytooid body lesion was evident by retinal edema.

Capillary occlusions in the nerve-fiber layer sufficed to produce cytooid body lesions.

Experimental hypertension in animals:

Garner et al. (1975) [88] observed many points of fluorescein leakage on terminal retinal arterioles as the earliest abnormality in an experimental hypertension study in the monkey. Such leaking points have always been present in correlation to CWSs.

"FIPTs" and CWSs

In animal experiments, Hayreh et al. (1986) [115] observed multiple punctate foci of fluorescein leakage from dilated precapillary retinal arterioles without focal retinal capillary obliteration. These "focal intraretinal periarteriolar transudates" ("FIPTs") lasted two to three weeks. They left no ophthalmoscopic, angiographic, or microvascular abnormality on resolution. "FIPTs" are a specific retinal lesion of malignant arterial hypertension only. "FIPTs" developed fully in

about one week and lasted for two to three weeks. In contrast, CWSs showed delayed or nonperfusion of the superficial retinal capillaries in the region of the lesion. CWSs lasted much longer than "FIPTs".

Experimental arterial hypertension

Hayreh et al. (1989) [117] showed CWSs due to arterial hypertension in experiments on monkeys. Fluorescein angiography of the retinal lesions revealed focal retinal capillary nonperfusion. The CWSs usually resolved within six weeks, leaving permanent obliteration of the retinal capillaries. During the initial stage of fluorescein angiography, retinal capillaries revealed nonperfusion around the CWSs. During the later stages, most of the CWSs showed slow, delayed filling of the retinal capillaries from the adjacent capillaries, and during the terminal stages of CWSs, permanent retinal capillary obliteration was demonstrated. Capillary obliteration progressed over time, so that prominent focal or extensive capillary obliteration later became obvious in those areas. They found a substantial correlation between the extent of retinal capillary obliteration and the extent and distribution of the CWSs.

Experimental radiation retinopathy

Irvine & Wood (1987) [130] produced radiation retinopathy in monkeys. The first change detected after radiation was focal loss of capillary endothelial cells and pericytes, and the first clinical sign was the appearance of CWSs 12 to 24 months after treatment. CWSs increased in number over the following four to eight months and then faded away. White arterioles and large areas of capillary nonperfusion remained.

Experiments with platelet and leukocyte aggregates in animals

Schroer et al. (1992) [288] used different microparticles injected into the ophthalmic artery of pigs. Injected, mixed aggregates containing platelets and leukocytes resulted in superficial and deep retinal infarctions. Large platelet aggregates caused arterial branch occlusion, whereas mixed and small platelet aggregates produced occlusion of small arterioles.

Arterial branch occlusion occurred immediately after injection of aggregates, resulting in retinal edema of the corresponding area. These vascular occlusions remained for about five to seven days. CWSs and hemorrhages were usually observed on the following day, lasting one to five days. Scheurer et al. (1992) [268] used leukocyte aggregates that produced CWSs and arterial branch occlusions with retinal edema in animal experiments. Aggregates 0.65-1.0 mm in size resulted in several CWSs, retinal edema, and arterial branch occlusions in two of five experiments.

Diabetic retinopathy in animal experiments

CWSs in diabetic retinopathy in monkeys were observed by Tso et al. (1988) [324] and Kim et al. (2004) [141]. Tso et al. (1988) found distinct arteriolar and venular occlusions in diabetic monkeys. Small multiple "focal intraretinal capillary leakage spots" ("FICALS") were revealed angiographically in association with the arterioles, capillaries, and venules in the arteriovenous phase. "FICALS" appeared as tiny yellowish dots in the retina of the posterior pole, appearing as globular

hyperfluorescent spots in the fluorescein angiogram. The "FICALS" shared several features with the above mentioned "focal intraretinal periarterial transudates" ("FIPT") in experimental hypertension, as observed by Hayreh et al. (1986) [115]. Tso et al. assumed that FICALS reflect focal damage to the endothelial cells, most frequently in the capillaries.

Experiments with elevation of intraocular pressure (IOP)

Anderson & Hendrickson (1974) [2] examined the changes in axoplasmic transport by elevating IOP. Injection with [³H] leucine into the vitreous of monkeys was carried out. Intraocular pressure was maintained for eight hours at certain levels between 15 and 105 mm Hg. With a slight elevation of IOP to achieve a perfusion pressure (PP) of 60 mm Hg there was partial obstruction of axoplasmic transport, which was more pronounced at a PP of 45 and 35 mm Hg. When IOP was elevated to only 25 mm Hg below mean femoral blood pressure, an abundant amount of label accumulated around the lamina cribrosa. The authors thus concluded that axoplasmic transport is affected by intraocular pressure, even at moderate elevations of IOP.

Minckler & Bunt (1977) [213] also supported the general concept that axoplasmic transport in the optic nerve head is sensitive to alterations in intraocular pressure.

The authors confirmed experimentally the general concept that intraocular pressure (IOP) can influence axoplasmic transport in the optic nerve head, particularly if high IOP causes reduced transport. Anderson (1979) [3] pointed out that slow axonal transport is impaired in both papilledema produced by intracranial balloons and in the disc swelling of experimental hypotony. When material is carried from the ganglion cell body (e.g. in the retina) to the synaptic ending (e.g. in the lateral geniculate body), rapid axonal transport requires a 10 cm distance for about six hours. Axoplasmic transport requires metabolic energy at every axon segment along the way.

McLeod et al. (1980) [205] studied pathological changes in the optic disc of monkeys five hours and several days after occlusion of the temporal short posterior ciliary arteries. Axonal swelling and organelle aggregation were demonstrated in the prelaminar region due to obstruction of rapid and slow orthograde axoplasmic transport. The pale swelling of the optic disc represented an accumulation of axoplasmic debris in retinal ganglion-cell axons.

5. DISEASES CAUSING EMBOLIZATION

CWSs in patients with fat embolism

Fat emboli due to fractures of long bones can cause obstruction of small retinal arteries, described by Urbanek (1934) [329], Pape (1964) [233], Kroll et al. (1981) [166], and Roden et al. (1989) [259].

Pape (1964) [233] emphasized the difference between Purtscher's retinopathy and fat embolism. The retinal fat embolism usually heals without any causing lasting damage. But in Purtscher's retinopathy, extreme late damage may occur, even blindness. Kroll et al. (1981) [166] observed multiple CWSs in the retina but no hemorrhages in a 19-year-old man after fat em-

bolism; they emphasized that conjunctival petechial hemorrhages can occur in patients with fat embolism, but not in Purtscher's retinopathy. Fischbein & Safir (1971) [81] emphasized that fat embolism is frequently confused with Purtscher's retinopathy, postulating that intravasation of marrow fat into the venous system is responsible for the clinical symptoms. CWSs are typical retinal findings at the posterior pole with or without hemorrhages. Madsen (1972) [185] found no venous stasis apparent in patients with fat embolism, in contrast to patients with Purtscher's retinopathy.

Amniotic fluid embolism

Amniotic fluid embolism is a serious complication of pregnancy resulting in death in the majority of patients.

Chang & Herbert (1984) [48] described bilateral retinal arteriolar occlusions in a 28-year-old mother who survived amniotic fluid embolism, observing an inferotemporal retinal branch arteriolar occlusion and refractile bodies with distal edema, along with CWSs and superficial nerve-fiber hemorrhages involving the superotemporal arcade.

6. COMPLICATIONS FOLLOWING EMBOLIZATION

Acute choroidal ischemia with partial retinal hypoperfusion after embolization

Schmidt et al. (1997) [276] found deeply localized retinal CWS-like spots in the temporal paramacular area and adjacent to the temporal retinal blood vessels after embolization of the ophthalmic artery with "Ethibloc" in neuroradiology. In addition, fluorescein angiography showed a vertical watershed-like zone close to the temporal border of the optic disc. This treatment was necessary to stop life-threatening epistaxis caused by an angioma extending from the nose to the soft tissue of the lower lid in a 32-year-old man.

Retinopathy and Horner's syndrome following coil embolization of an intracavernous carotid artery aneurysm.

Castillo et al. (2005) [46] observed multiple CWSs along the peripapillary area and temporal vascular arcades in a 29-year-old woman who underwent coil embolization of an intracavernous carotid artery aneurysm. In addition, pupillary miosis and mild ptosis of the right upper lid (Horner's syndrome) were noticed. Perimetry showed a superior arcuate scotoma and an inferonasal step in the right eye.

Talc embolization

Jampol & Rabb (1981) [133] described CWSs after acute talc embolization. Fluorescein angiography revealed precapillary arteriolar obstruction and capillary-bed nonperfusion.

7. HISTOLOGY OF CWSs

Histological examination revealed "cytoid bodies" in the vicinity of a CWS. Distensions of axon cylinders was described in the retinal nerve-fibers by Wilbrand & Saenger (1909) [340] in a comprehensive treatise on retinal diseases. They observed various sizes ranging from spindle-shaped to club-shaped distensions as large as ganglion cells in the nerve-fibers. Some of the

swellings contained roundish or irregularly brilliant corpuscles. These circumscribed distensions were sometimes found tightly packed together in small elevated clumps. The ophthalmoscopic correlates were bright white non-transparent spots, located exclusively in the nerve-fiber layer, mostly in their internal layers. They sometimes covered retinal vessels. Goerlitz (1920) [96] also called attention to globular or oval compactations in the nerve-fiber layer. Gipner (1930) [94] postulated that CWSs are due to varicose, swollen, and degenerative nerve-fibers. They usually appeared in the early stages of retinitis. J.S. Friedenwald (1949) [86] found that cytooid bodies corresponded to areas in which the retinal nerve-fiber layer was swollen, revealing a central eosinophile globule.

Diezel & Willert (1961) [64] observed such nerve-fiber lesions histologically. Christensen (1958) [54] emphasized that the cytooid body is the "principal constituent of the CWS". CWSs are non-specific deposits of acellular origin, which probably occur following damage to the terminal arterioles in the denser portion of the nerve-fiber layer. An inner zone with fibrin or fibrinoid and an outer zone with swollen precipitated ground substance were distinguished. Electron-microscopy revealed that cytooid bodies are the swollen ends of disrupted nerve axons.

Wolter (1959) [342] found that cytooid bodies ("Cajal's nodules") were terminal nerve-fiber swellings of Cajal at different stages of their development.

Ashton et al. (1968a) [14] also found histologically and ultrastructurally the characteristic finding of cytooid bodies as focal aggregations of globular structures within the retinal nerve-fiber layer. Dollery & Hodge (1963) [68] described microaneurysms as frequently outlined in the vicinity of CWSs by fluorescein angiography. Microaneurysms were more common at the edge of a CWS. They sometimes form a partial or complete ring around the lesion's periphery. Small aneurysms 15-30 microns in diameter clear up quickly and may disappear within two weeks. Larger aneurysms up to 90 microns in diameter last longer and may still be present after four to six weeks. Other vascular abnormalities such as tortuous veins occur in the vicinity of CWSs.

Ashton & Harry (1963) [12] observed cytooid bodies in clusters in the nerve-fiber layer of the retina in CWSs, but CWSs did not always contain them. A single cytooid body represented the bulbous end of a swollen nerve-fiber. They also observed that the pseudocyttoplasm consisted of numerous mitochondria with many vesicles and granules. The pseudocyttoplasm is formed by axoplasm and it is a component of the terminal swelling of the axon. Shakib & Ashton (1966) [295] noticed that ischemia of only a few minutes' duration resulted in axonal swelling that developed into nodular or varicose enlargements. Shakib & Ashton (1966) [295] believed that a CWS is a focal ischemic lesion of the retina's inner layers, and that the cytooid body was formed by the terminal bulbous swelling of an axon, shown by electron-microscopy.

Duke-Elder (1967) [72] demonstrated that cytooid bodies occur in all conditions that impair the vitality of the nerve-fibers in the retina's inner layer. Electron-microscope studies have shown that they are de-

rived from axonal degeneration. Garner & Ashton (1971) [87] observed large numbers of markedly swollen nerve-fibers with intact axonal membranes in the nerve-fiber layer. There were focal swellings of the axons with formed fusiform or torpedo-like enlargements or terminal nodes, and numerous swollen mitochondria, microcysts, dense bodies, granular material and proliferating neurofilaments were found in those axonal swellings.

Pseudonucleus

The pseudonucleus in a cytoid body was thought to consist of aggregated elements within the swollen axoplasm (Ashton & Harry 1963) [12].

Shakib & Ashton (1966) [295] argued that the pseudonucleus can be formed by the proliferating and degenerating structures of the bulbous axoplasm. They may consist of neurofilaments, mitochondria, dense bodies, or membranous whorls which become clumped after ischemia. Garner & Klintworth (1994) [90] showed that cytoid bodies are the swollen ends of disrupted nerve axons by electron-microscopy. Furthermore, they found that the pseudonucleus consists of amorphous electron-dense material considered to have derived from the lipid-protein residues of degenerate cytoplasmic organelles.

Endothelial cause

Ashton & Harry (1963) [12] discussed arteriolar spasm as the precipitating cause of arteriolar occlusion, demonstrating that CWSs might arise directly from altered permeability of the endothelium in arterial hypertension. Such arteriolar change may thus be another manifestation of endothelial injury, and not the cause of CWS. Graham (1990) [101] also emphasized that CWSs are due to abnormalities of the vascular endothelium in most cases. The question arose whether a local specific immune reaction against endothelial cells can occur in isolation, since anti-endothelial cell antibodies have been demonstrated in the serum of patients with inflammatory vasculitis.

Cytoid bodies in the optic nerve

Wolter & Liss (1957) [341] described histologically cytoid bodies in the optic nerve in a patient who showed primary optic atrophy, assuming that cytoid bodies may have developed from terminal swellings of nerve-fiber stumps.

8. COLOUR OF CWSs

Wolter (1959) [342] assumed that the accumulation of nerve-fiber swellings, together with surrounding edema of the nerve-fiber layer, can be considered as causing the whitish colour of CWSs.

CWSs first appear as a gray-white film which change into a white patch over three to 14 days, then becoming granular and disappearing (Hodge & Dollery 1964) [122]. Ashton (1972) [16] argued that the lesion's white opacity is caused by closure of the dependent capillary circulation, nerve-fiber swelling, and proliferation of their organelles. McLeod (1975) [199] emphasized that the intense retinal "whiteness" of small CWSs and at the periphery of larger areas of retinal ischemia repre-

sents gross, local axonal distension secondary to the cessation of axoplasmic flow. McLeod (1976a) [200] explained that the dense white swelling of the inner retina in CWSs is caused by the aggregation of mitochondria at the site of axonal interruption.

In larger lesions, a central grayish zone of CWSs is visible which represents axonal ganglion cell necrosis and axoplasm accumulation. Edema fluid accounts for the more opaque, whitish swelling at the margins (Garner & Klintworth (1994) [90]).

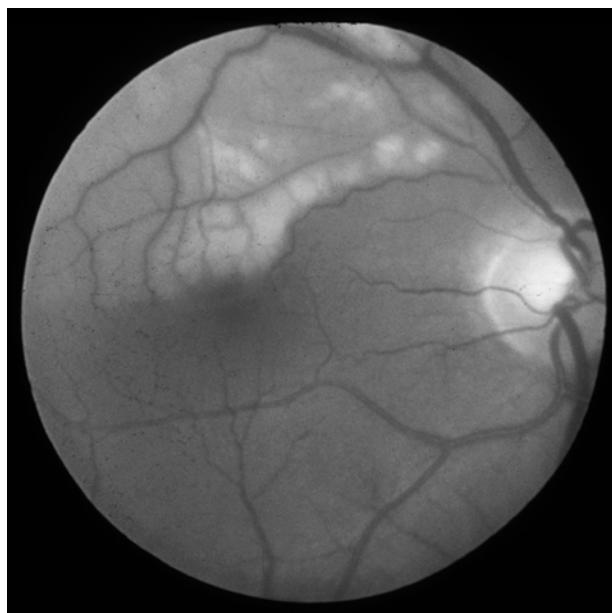


Fig. 1. RE: Branch retinal artery occlusion of the superior temporal artery with CWSs, pronounced at the margin of the edema in a 45-year-old male.



Fig. 2. RE: Branch retinal artery occlusion of the inferior temporal artery with CWSs at the upper margin of the edema in a 59-year-old male.

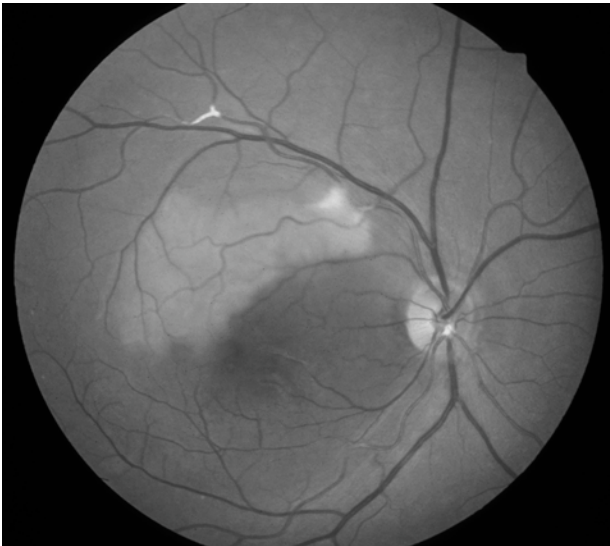


Fig. 3. RE: Branch retinal artery occlusion of the superior temporal artery with CWSs at the upper margin of the edema in a 44-year-old male.

9. LOCATION OF CWSs

Ashton & Harry (1963) [12] described significant features of CWSs as their superficial situation, extending rarely deep into the vessels, their restriction to the posterior segment of the fundus (usually within a few disc diameters of the disc), their relatively small size (of about a third of the disc), and their limited number (of rarely more than 10).

Deeper white lesions should not be confounded with CWSs. The deeper spots are smaller, rounder and do not have the fluffy, striated and elongated appearance of CWSs. Instead of containing cytooid bodies in an edematous area, the deeper lesions reveal a degeneration of the retinal cells (Duke-Elder 1967) [72].

Location of CWSs

Many authors described CWSs only in the posterior pole of the fundus (Brown & Magargal (1988) [40], Garner & Klintworth (1994) [90], Folberg & Bernardino (1998) [83], Walsh et al. (1998) [337]. CWSs were located around the disc by Leishman (1957) [174]. McMichael & Dollery (1963) [208], emphasized that the CWSs usually lie close to the main vessel groups within three diameters of the disc. J. S. Friedenwald (1949) [86] observed that the cytooid bodies are usually located between the terminal bifurcation of a terminal arteriole in the specimens. Hodge & Dollery (1964) [122] found the largest CWSs about two mm in diameter on the retinal surface; the smallest were about 100 microns in diameter. CWSs usually lie close to the main vessel groups in the eye, within three or four diameters from the disc. Tso & Jampol (1990) [325] noted that most frequently the longitudinal axis of the CWSs is found at a right angle to the direction of the nerve-fiber layers. CWSs are most often located on the surface to the retinal blood vessels. Walsh et al. (1998) [337] observed CWSs in the distribution of radial peripapillary capillary bed. They were localized within the nerve-fiber layer, often involving the underlying ganglion cells.

CWSs close to veins

J. S. Friedenwald (1949) [86] reported seeing CWSs usually on the venous side of the lesion, and that they are most prominent in those lesions in which the cytooid bodies themselves are relatively feebly stained. Hammami & Streiff (1973) [110] observed that CWSs were mainly located adjacent to retinal veins in a patient with SLE. Hayreh et al. (1989) [117] noted that the lesions are found predominantly in the venous capillary system in diabetics.

CWSs in close relation to a retinal arteriole

Leishman (1957) [174] reported that superficial CWSs may be scattered over the fundus, lying usually in close relation to a small arteriole. Ashton & Harry (1963) [12] observed that CWSs are more associated with arteries than to veins. Vascular dilatation and microaneurysms were commonly seen at the margins of CWSs. Stucchi & Ménestrier (1961) [316] described CWSs adjacent to retinal arteries in a patient with eye muscle pareses due to pansinusitis. They also enumerate various systemic diseases accompanied by retinal CWSs such as collagenoses, diabetes, liver and infectious diseases, and malignomas.

CWS associated with capillary nonperfusion

Kohner et al. (1969) [157] noticed that CWS have always been associated with areas of capillary nonperfusion. Fluorescein angiography revealed that CWSs were associated with arteriolar occlusion in an area of capillary closure, being surrounded by abnormal dilated capillaries. A high-flow arteriovenous shunt vessel was found in one patient. They believed that capillary abnormalities precede the development of arteriolar occlusion necessary for the development of CWSs. However, slow occlusion of arterioles may cause a gradual ischemic necrosis without development of CWSs.

10. ONLY ONE CWS

The observation of a single CWS, even in the eye of a person in ostensibly good health, is an extremely important clinical sign (Brown et al. 1985) [39]. One CWS in an otherwise normal fundus should lead to additional examinations to ascertain systemic etiologic factors. An isolated CWS is unusual and may herald a severe systemic disease (Graham 1990) [101]. One CWS may occur for instance in patients with diabetes and/or hypertension. Wolter & Boldt (1963) [343] described one CWS in a 41-year-old patient with scleroderma perforans and iridocyclitis, with no evidence of rheumatoid arthritis or collagen disease.

Gold et al. (1972) [97] examined 61 patients, observing a solitary CWS in one eye each of two patients with SLE. One of them was hypertensive and had arteriolar narrowing; the other was normotensive.

Graham et al. (1985) [100] observed a normal optic disc in a 16-year-old youth with SLE in the right eye and normal retinal vessels with a CWS temporal to the optic disc. His left optic disc was normal.

Laibovitz (1982) [171] found a single CWS in one eye in a 46-year-old woman with iron deficiency anemia causing reversible disc edema. Selsky & Nirankari (1985) [292] reported a 66-year-old woman who deve-

loped complete blindness in both eyes due to giant-cell arteritis (GCA). The retinal examination revealed one CWS in her right eye, but no other abnormalities in the fundus. Hayreh (1987) [116] found only one CWS in a patient with post-hemorrhagic amaurosis and anemia.

A 73-year-old woman with the characteristic signs and symptoms of biopsy-proved GCA complained about scintillation of her left eye. That eye's retina revealed one CWS temporal and adjacent to the optic disc. Visual acuity and visual field were normal (Schmidt 1995) [274]. Schmidt (1996) [275] observed one small CWS superior to the optic disc in a 75-year-old woman with bilateral anterior ischemic optic neuropathy (AION) and small peripapillary hemorrhages.

Remky & Arend (2000) [257] examined four patients complaining of blurred vision or scotomas with sudden onset, two of whom were pregnant. Ophthalmoscopy revealed single isolated white spots in the temporal arcades in three patients and in the papillomacular bundle in one patient. No systemic disease was found in these four patients. The authors suggested that isolated CWSs may occur without serious systemic diseases in otherwise healthy subjects. The diagnosis of an acute inflammatory retinochoroidal lesion also should be considered.

Cohen & Gardner (2006) [58] reported on bilateral rare CWSs in a 71-year-old woman. A fluorescein angiogram revealed delayed choroidal filling, in one eye, even at 4 minutes the temporal choroid did not fill with dye. The eye eventually developed hyperpigmentation in the nonperfused area.

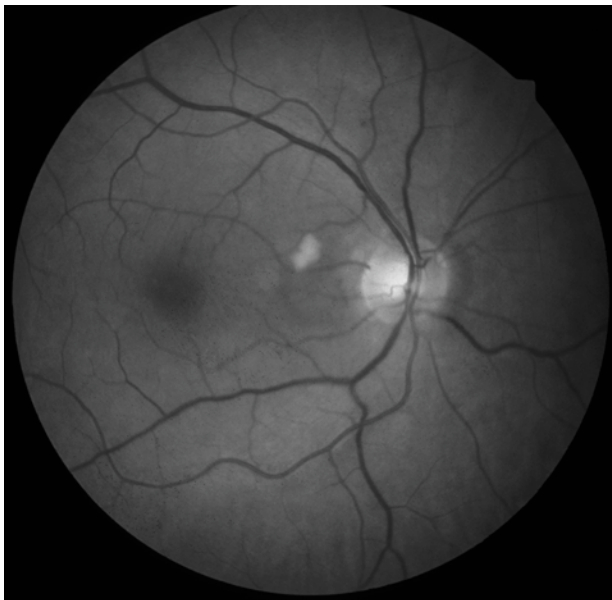


Fig. 4. RE. CWS in a 49-year-old man with arterial hypertension.

11. DEVELOPMENT AND REGRESSION: THE LIFE CYCLE OF CWSs

Ashton & Harry (1963) [12] reported that CWSs developed 80 to 90 days after carotid ligation.

J. S. Friedenwald (1949) [86] observed that CWSs usually disappear in two to four weeks. Unger (1957) [328] reported on two patients with pheochromocytoma and marked hypertensive retinopathy with optic disc swelling. Blood pressure returned to normal after surgery. CWSs regressed slowly, but in one patient seven weeks postoperatively, slight residues remained visible. Ellis & Fonken (1966) [76] stated that CWSs in glomerulonephritis generally cleared during the initial two or three weeks after renal transplantation. Such lesions were seldom present three to five weeks postoperatively. Hodge & Dollery (1964) [122], observed that small CWSs disappear in two weeks, but larger ones in eight to ten weeks. Dollery et al. (1966) [69] reported a short life cycle of porcine CWS: a grey patch in the retina appeared within a few minutes after embolization, and the CWS had developed fully within 24 to 48 hours, then fading rapidly and disappearing within seven to 14 days. However, human lesions reveal a much longer life cycle. Many CWSs in humans begin as a small gelatinous white area, becoming larger within 48 to 72 h. The lesion disappears in the following six to 12 weeks. Matas (1977) [192] pointed out that CWSs appear suddenly and usually disappear in four to 12 weeks, leaving no ophthalmoscopically-visible scar, although the damage they cause can be detected microscopically. Hayreh et al. (1989) [117] observed that CWSs can take weeks to resolve, usually over three and under six weeks in animals. As the old spots resolved, new ones appeared from time to time - even up to about ten months after renal artery clamping in some one-kidney animals. Tso & Jampol (1990) [325] found that once CWSs disappeared, the retina may appear thin, with the internal limiting membrane appearing shiny and irregular. The authors referred to these areas as "macular depressions". They represent the local loss of the inner retinal elements from infarction.

Healing phase of CWSs

Garner & Klintworth (1994) [90], reported that necrotic debris is removed through autolysis and phagocytosis in the healing phase of CWSs, eventually forming a glial scar. The nonperfused capillaries may reopen.

12. METHODS FOR RETINAL EXAMINATION

Fluorescein angiography: vascular lesions accompanying CWSs

Hodge & Dollery (1964) [122] observed vascular lesions, usually microaneurysms, visible on fluorescein angiography in most of the CWSs. Microaneurysms, dilated capillaries, and tortuous small venules have been found in association with most CWSs. In the minutes following dye injection, over 90% of CWSs became fluorescent. Some were arranged like strings of beads along the course of tiny venules, others were connected to veins through minute channels. The great majority of the CWSs they studied were in patients with severe hypertension. Four of six patients with untreated malignant hypertension showed precipitous early leakage from point sources. The patient with the most florid lesions of that type had masses of

CWSs and severe retinal edema as well. Dollery et al. (1966) [69] found that characteristic fluorescence angiographic features of CWSs in hypertension are localized, diffuse leaking points on or near feeding arterioles. Jampol & Rabb (1981) [133] also pointed out that, in the late phase of the fluorescein angiogram, leakage around the CWS margins occurs, often from dilated capillaries and microaneurysms. Tso et al. (1988) [324] noticed that CWSs sometimes appear hypofluorescent in the early phase of fluorescein angiography, becoming hyperfluorescent in the late phase; those were definitive signs of retinal ischemia. Garner & Klintworth (1994) [90], found that preceding or associated vascular leakage at the site of a CWS were not uncommon in fluorescein angiography. Pache et al. (2002) [230] revealed angiographically that all their patients with arterial hypertension demonstrated a rarefaction of the perifoveal capillary bed and a decrease in capillary blood velocity compared to normal subjects. CWSs occurred in advanced stages of hypertensive retinopathy.

Duke-Elder (1967) [72] stressed that the first change seen is a leakage of fluorescein from the minute vessels, followed by devascularization around the cotton-wool spots.

Visual fields in patients with CWSs

Bek & Lund-Andersen (1991) [24] examined the visual fields in the eyes of 14 diabetic patients. Retinal CWSs were associated with localised non-arcuate scotoma. The CWSs disappeared in four eyes within three months of the first examination; in two of those patients, the corresponding scotomata disappeared along with the morphological lesions. In contrast to their observation, Snady-McCoy & Morse (1985) [304] described their findings in two patients, a 28-year-old woman and a 23-year-old man suffering from severe visual loss due to acute pancreatitis. Both patients' retinas revealed bilateral CWSs and hemorrhages, predominantly in the posterior pole. Follow-up observation showed reperfusion of previously-occluded retinal vessels by fluorescein angiography. But visual fields demonstrated scotomas corresponding to the areas of the earlier CWSs. Walsh et al. (1998) [337] reported that CWSs typically resolve in four to six weeks, leaving a corresponding nerve-fiber layer defect.

Chaum et al. (2001) [49] emphasized that visual fields usually appear normal after small retinal infarcts by CWSs. CWSs rarely cause significant visual field loss. However, a large CWS in a 34-year-old woman caused a fiber bundle visual field and afferent pupillary defects that remained after the CWS had disappeared. The "giant" CWS was located right next to the optic nerve.

Glaucoma

Chihara & Honda (1991) [51] found that the degree of visual field defects in eyes with CWSs resembled to that found in patients with primary open-angle glaucoma. Changes in optic-disc topography in 26 eyes with CWSs displayed defects in the retinal nerve-fiber layer and resembled 31 eyes with early primary open-angle glaucoma.

Acute and resolved CWSs revealed in high-resolution optical coherence tomography (OCT)

Kozak et al. (2006/2007) [162/163] measured the hyperreflective sign in the area of acute CWSs and in the area of resolved CWSs with high-resolution optical coherence tomography (OCT). They examined the CWSs in 12 patients with diabetic retinopathy, ten with HIV retinopathy, three with hypertensive retinopathy, three with branch retinal vein occlusion, two with uveitis and one with radiation retinopathy, detecting a hyperreflective pattern in acute CWSs. Later, as they became ophthalmoscopically invisible, the hyperreflectivity remained in the area of previous CWSs. Even three months after the disappearance of CWSs, slightly hyperreflective nodules were seen at the sites of previous CWSs. The authors hypothesized that hyperreflective nodi in OCT images represent glial CWS transformation.

13. DIFFERENT DISEASES WITH CWSs

CWSs are non-specific, as they occur in association with various diseases (Table 1).

Table 1. Conditions associated with cotton-wool spots.

Vascular diseases

- Diabetes mellitus
- Systemic arterial hypertension
- Incomplete CRAO
- Retinal vein obstruction
- Carotid artery obstruction
- Aortic arch syndromes (pulseless disease)
- Radiation retinopathy
- High altitude retinopathy

Collagen vascular and immunological diseases

- Dermatomyositis
- Systemic lupus erythematosus
- Dermatomyositis
- Polyarteritis nodosa
- Polymyositis
- Scleroderma
- Giant cell arteritis
- Waldenström's macroglobulinemia
- Wegener's granulomatosis

Cardiac valvular disease

- Mitral valve prolapse
- Rheumatic heart disease
- Endocarditis

Inflammations

- Acquired immunodeficiency syndrome (Aids)
- Acute pancreatitis
- Intravenous drug abuse
- Leptospirosis
- Onchocerciasis
- Rocky Mountain spotted fever
- Septicemia

Malignancy

- Leukemia
- Metastatic carcinoma

Additional diseases

- Severe anemia
- Acute blood loss
- Papilledema
- Papillitis
- Trauma
- Dysproteinemias

Table 2. Causes of Cotton-wool spot (Graham 1990) [101].

Abnormalities of vascular endothelium	Arteriosclerosis Diabetes mellitus Hypertension Systemic vasculitis (SLE, PAN, GCA, scleroderma) Radiation retinopathy Human immunodeficiency virus
Abnormal erythrocytes Unusual emboli	Haemoglobinopathies Fat Talc

Occluded arterioles

Shakib & Ashton (1966) [295] stressed that occluded arterioles have been demonstrated in hypertensive retinopathy; and may be assumed to cause CWSs in leukemia, fat emboli, or sickle-cell anemia.

13.1 Associated systemic diseases

Dollery & Hodge (1963) [68], mentioned the multiple causes, as CWSs arise in severe anemia, after gastrointestinal hemorrhages, after carotid artery ligation, and in hypertensives and diabetics.

Wilbrand & Saenger (1909) [340] wrote a chapter on retinal white spots, enumerating many different diseases in which they coincide: anemia due to blood loss due to gastric ulcer, pernicious anemia, leukemia, diabetes, syphilis, sepsis, thrombopenia (Werlhof's disease), liver diseases (hepatitis luetica, hepatic cirrhosis, liver cancer, hepatic abscess), stomach cancer, quininism, phosphorism, and tuberculosis.

Brown et al. (1985) [39] found one or more associated systemic diseases in 96% (23 / 24) of patients with CWSs.

Storimans et al. (1991) [313] reported a new autosomal dominant vascular retinopathy syndrome in a large family with 61 members who were examined ophthalmoscopically. In 22 persons a microangiopathy with areas of capillary non-perfusion, CWSs and hemorrhages were observed. In addition, 31 out of 110 family members had migraine, 34 patients had Raynaud's phenomenon, and 32 persons had mental changes.

Matsubara et al. (1998) [193] observed bilateral extensive retinal edema with numerous CWSs in a 7-year-old girl who suffered from hemophagocytic lymphohistiocytosis in association with congenital dysfibrinogenemia. The findings were explained by cellular infiltrations and increase in cytokines around retinal microvessels leading to extensive obstruction of retinal arterioles resulting in ischemia. It was emphasized that this serious complication could be preventable by early institution of chemotherapy of the disease.

Non-hypertensive conditions

Ashton & Harry (1963) [12] enumerated the occurrence of CWSs in non-hypertensive conditions. Emboli can produce the same type of lesion, or for example fat emboli in Purtscher's traumatic retinopathy, bacterial emboli in septic retinitis, and subacute bacterial endocarditis. In addition, CWSs can occur due to vascular occlusion, as seen in leukemia.

13.2 Ischemia

Ischemia as primary cause for CWSs development

Ischemia most likely represents local damage in the nerve-fiber layer (Wolter 1959) [342]. Wolter & Moorman (1966) [344] described axonal necrotic foci after photocoagulation burns in the retina, finding terminal swellings on numerous nerve stumps at the proximal and distal aspects of the burns. Altered neurons due to capillary obliteration in the inner nerve-fiber layer of the retina were observed. Histological examinations showed an accumulation of cytooid bodies. J.S. Friedenwald (1949) [86] maintained that arteriolar spasm can induce a retinal infarct.

Duke-Elder (1967) [72] explained that CWSs essentially consist of altered neurons resulting from functional obliteration of the capillaries, representing a focal reaction of injured but still-living cells. He emphasized that the ischemic lesion due to acute occlusion of a focal area of small vessels is regarded as the common factor in the appearance of a CWS. As local factors, several causes are mentioned: an infarct due to fibrinoid arteriolar degeneration, or a thrombus, or micro-embolism, or a sudden decrease in retinal arteriolar pressure.

Ashton et al. (1968a) [14] found CWSs in retinal territories supplied by occluded pre-capillary arterioles; the non-functioning capillaries in those areas showed degenerative changes. Hayreh et al. (1989) [117] concluded that CWSs are due to occlusion of the terminal retinal arterioles with focal nonperfusion of the retinal capillaries in their distribution, resulting in acute focal inner retinal ischemia. They therefore recommended calling these lesions "inner retinal ischemic spot (IRIS)" instead of CWSs.

Ocular ischemic syndrome

Atebara & Brown (1998) [17] described essential ocular symptoms in ischemia. Patients complain about visual loss, eye pain, difficulty of light adaptation, or

Table 3. Signs of Ocular Ischemic Syndrome and the frequency of their occurrence (Brown & Magargal 1988) [40].

Signs	Number of eyes (n = 51) (Percentage)
Anterior segment	
Rubeosis iridis	34 (67)
Neovascular glaucoma	18 (35)
Anterior uveitis	9 (18)
Posterior segment	
Narrowed retinal arteries	most
Dilated retinal veins	most
Retinal hemorrhages	41 (80)
Neovascularization of the disc	18 (35)
Neovascularization of the retina	4 (8)
Cherry-red spot	6 (12)
Cotton-wool spot	3 (6)
Spontaneous retinal artery pulsations	2 (4)
Cholesterol emboli	2 (4)
Anterior ischemic optic neuropathy	1 (2)

they may be completely asymptomatic. The signs are anterior segment inflammation, iris neovascularization, retinal venous dilation, midperipheral intraretinal hemorrhages, CWSs, macular edema, or posterior segment neovascularization. Andersen (1978) [1] found that CWSs are often surrounded by microaneurysms and hemorrhages indicating that they react to ischemia.

Brown & Magargal (1988) [40] reported an ocular ischemic syndrome attributable to severe carotid artery obstruction in their study of 43 patients.

The authors stressed that microaneurysms were frequently observed, particularly by fluorescein angiography. CWSs were found in three of 51 eyes. They were also associated with irregularly-dilated retinal veins in each patient and were detected only in the posterior pole.

Ischemic retinopathy due to carbon monoxide poisoning

Carbon monoxide combines hemoglobin to form carboxyhemoglobin. Carboxyhemoglobin cannot transport oxygen, leading to signs of ischemia.

Bilchik et al. (1971) [27] described the ocular findings of three family members exposed chronically to high levels of carbon monoxide in their home.

The 49-year-old mother and her 11-year-old son had bilateral swollen discs with venous tortuosity and engorgement, flame-shaped and round retinal hemorrhages, CWSs, and areas of retinal edema. The father had hemorrhages and CWSs but normal discs.

Disc swelling

McLeod (1975) [199] explained that the pale optic disc swelling in ischemic optic neuropathy is caused by the cessation of orthograde axoplasmic flow in ganglion-cell axons. An accumulation of axoplasmic debris at the optic disc has also been observed in some patients with central retinal vein occlusion (CRVO) (McLeod (1976a) [200]).

Retinal infarction

Several authors assumed that CWSs are the clinical manifestation of focal infarcts (microinfarcts) in the retinal nerve-fiber layer: J.S. Friedenwald (1949) [86], Wolter (1959) [342], Matas (1977) [192], Greite (1983) [103], Spencer (1985) [307], Garner & Klintworth (1994) [90], Naumann (1997) [221], Folberg & Bernardino (1998) [83], Chaum et al. (2001) [49].

Garner & Klintworth (1994) [90] argued that CWSs can be regarded as microinfarcts. They suggested classifying them as pre-infarcts, since there is a limited capacity for recovery.

Garner & Ashton (1971) [87], reported that CWSs are caused by focal ischemia from arteriolar occlusion. Arteriolar occlusion leading to CWSs has been demonstrated in various retinopathies. In experiments injecting artificial emboli, Ashton & Henkind (1965) observed arterial occlusions accompanied by the development of CWSs. Arteriolar occlusion has also been demonstrated in animals under experimental hypertension.

Dollery et al. (1966) [69] reported that in hypertensive retinopathy, CWSs revealed circumferential microaneurysms and central capillary closure. Dilated capillaries and tortuous small venules were observed in 84% of the CWSs.

Matas (1977) [192] described fusiform swelling in the nerve-fiber layer in which a localized ischemic infarct resulted in Wallerian degeneration in several nerve-fibers. These degenerative axonal changes result in cytoid body formation. Folberg & Bernardino (1998) [83] pointed out that occlusion of the most superficial radially-oriented peripapillary capillaries has been implicated in the pathogenesis of CWSs, and they often observed localized, diffuse leaking points on or near feeding arterioles.

In contrast to all experimental findings, McLeod (2005) [207] detected that CWSs should be regarded as localised accumulations of axoplasmic debris, and not retinal fiber layer infarcts.

13.3 CWS occurrence in diabetic retinopathy

Sprafka et al. (1990) [308] pointed out that patients with retinal ischemia as in diabetic preproliferative retinopathy show CWSs and capillary nonperfusion mainly visible on fluorescein angiography. Kohner et al. (1998) [158] found marked diabetic retinopathy with CWSs or intraretinal microvascular abnormalities in 8% of men and 4% of women.

The frequency of CWSs in diabetic retinopathy depends on the severity and duration of the disease. Garner (1993) [89] stated histologically that increasing capillary closure was linked to CWSs.

McLeod (2005) [207] observed CWSs forming a C-shaped chain nasal to the disc and around the macula in pre-proliferative diabetic retinopathy, where they constitute "sentinels" of ischemia affecting the entire retinal mid-periphery. McLeod argued that polymorphous CWSs evolving during acute panretinal hypoperfusion represent "sentinels" of an ischemic penumbra.

Cytoid bodies, considered clinically as CWSs, appear as a result of the arteriolar changes in diabetic retinopathy. Precapillary arterioles were narrowed with gradual occlusion of their lumina (Ashton (1959) [10]. Avascular areas were constantly found in the vicinity

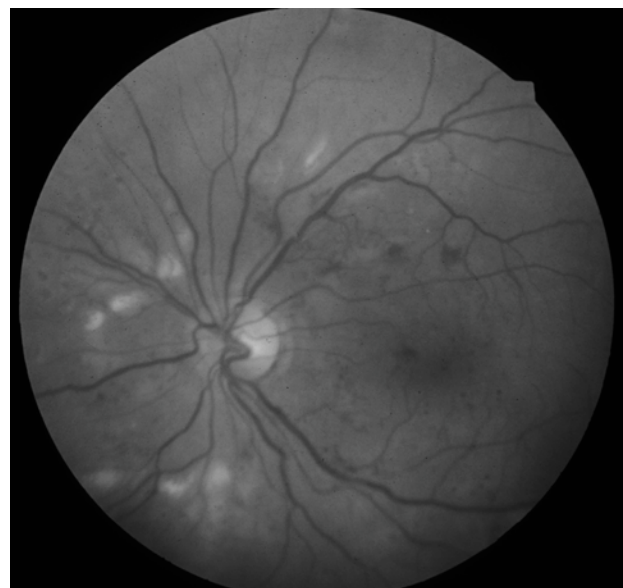


Fig. 5. Diabetic retinopathy with CWSs, showing a nasal semicircle in a 62-year-old male.

of the retinal arteries (Ashton (1953) [9]. CWSs may occur in diabetic patients, either isolated or associated with microaneurysms (Roy et al. 1986) [263].

Duration of diabetes and CWS occurrence

In diabetic patients, CWSs were documented after 14 years of disease in 8.6% of males and 6.8% of females opposed to hard exudates, which were found in 30% of the males and 27.2% in females (World Health Organisation 1985) [346]. Klein et al. (1987) [150] found CWSs in about 15% of patients taking insulin, but in only 5.4% of older-onset persons not taking insulin. Lesion severity as found in younger-onset persons to be consistently associated with longer duration of diabetes, and with the presence of proteinuria in older-onset persons.



Fig. 6. RE: Retinal infarction adjacent to the macula in a 28-year-old male with diabetes mellitus.

Appearance of CWSs independent from blood pressure (BP) in diabetes

In some studies on diabetic retinopathy, the appearance of CWSs has been reported to be independent from blood pressure (Andersen 1978 [1], Körner & Körner 1988) [159]. Harrold (1971) [112] found CWSs in patients with diabetic retinopathy in 50% of eyes from the hypertensive group and 51% from the normotensive group. Bek & Helgesen (2001) [25] compared diabetics in a study group who revealed significantly more microaneurysms, hemorrhages and with significantly higher blood pressure than those in the control group. However, the number of CWSs and their regional distribution did not differ significantly between patients in the study and control groups.

Influence of hypertension in diabetics

Black (1981) [31], reported on a 26-year-old male with insulin-dependent diabetes who underwent liver and

pancreas transplantation. Five months later, the patient complained about visual disturbances; an increase in the number of microaneurysms, hemorrhages, and CWSs were diagnosed. The patient was also hypertensive. The hypertension was treated, and the retinopathy largely resolved over the subsequent two months. This observation highlights hypertension's role in retinal ischemia.

Matthews et al. (2004) [194] reported on 1,148 hypertensive patients with type-2 diabetes mellitus. 758 patients were allocated to strict blood pressure control treatment and 390 were to laxer blood pressure control monitoring. 4.5 years after randomization, they found a highly significant difference in the microaneurysm count, with 23.3% in the strict BP control group and 33.5% in the laxer group. CWSs increased in both groups, but less so in the strict BP control group, who presented had fewer CWSs at 7.5 years.

CWSs despite intensified insulin treatment

Brinchmann-Hansen et al. (1988) [38] examined 45 diabetic patients who had been randomly assigned to treatment with continuous subcutaneous insulin perfusion (CSII), multiple injections (MI), and conventional insulin treatment (CIT). CWSs appeared in half of them on CSII and MI within six months, but not in the CIT patients. The authors assumed that increased retinal blood flow and vasodilatation could be important in the progression of diabetic retinopathy. Schmidt et al. (1994) [273] reported a progressive proliferative retinopathy despite normoglycemia requiring intensive panretinal photocoagulation in a 26-year-old type-1 diabetic male one year after pancreas transplantation. However, despite intensive retinal photocoagulation, vitreous hemorrhages and retinal neovascularization together with CWSs and distinct venous beading occurred. The patient was a heavy smoker, which may have played an at least partial role in the morbid retina which got so much worse.

Table 4. Isolated Cotton-Wool spots (Graham 1990) [101].

Cause	Investigation
1. Systemic vasculitis	ESR
	Antinuclear antibodies
plus SLE	Anti DNA antibodies
PAN	Immunoglobullins
	Eosinophil count
GCA	Temporal artery biopsy
	C reactive protein
2. Aids	HIV antibody
3. "Nil obvious"	Blood pressure
	Blood glucose
	Smoking habits

Huge CWSs in diabetic retinopathy

Egerer & Freyler (1973) [74] described atypical CWSs in four patients with diabetic retinopathy. The most striking characteristic distinguishing them from typical CWSs was their size, which ranged between two to four disc diameters. These huge CWSs developed after

stenosis of a first order retinal arteriole at the point at which it emerged from the parent arterial branch.

Synergism between diabetic and radiation retinopathy: case report and review

Viebahn et al. (1991) [331] described the development of radiation retinopathy with CWSs, hemorrhages and edema in a 54-year-old woman with breast cancer and minimal diabetic retinopathy. A fulminant retinopathy occurred within nine months of external beam radiation (3000 rads in fraction of 200 rads).

Six patients with radiation retinopathy with CWSs were successfully treated with intravitreal bevacizumab for reduction of the Vascular Endothelial Growth Factor (VEGF) by Finger & Chin (2007) [80]. Best-corrected visual acuity improved in two patients and was stable in four patients. Hemorrhages and retinal edema were reduced after treatment.

13.4 Hypertensive retinopathy

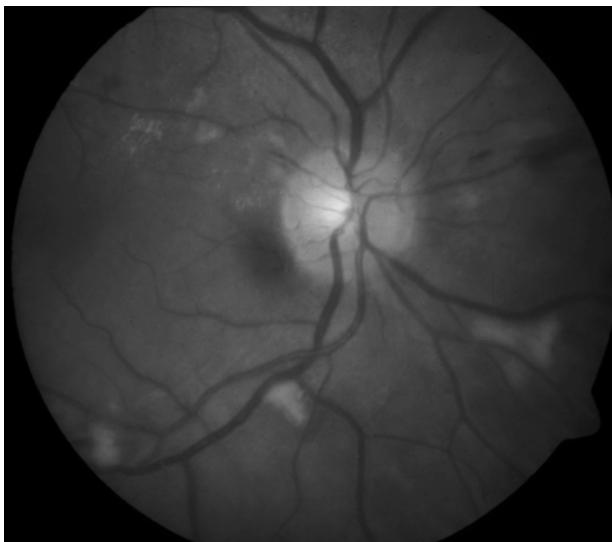


Fig. 7. CWSs adjacent to retinal vessels in a 40-year-old woman with arterial hypertension.

Liebreich (1859) [178] first mentioned roundish, bright, milky-white, slightly elevated retinal spots in patients with chronic nephropathy (Bright's disease). Bull (1886) [41] described retinal changes in 103 patients with Bright's disease, of whom 46 suffered binocular hemorrhages. He also found white lines along the arteries and papillary swelling.

Wilbrand & Saenger (1909) [340] described retinal white spots which occurred in "albuminuric retinitis" predominantly. They observed during follow-up that the spots extended, rather than becoming more numerous. Volhard & Fahr (1914) [334] also noticed hemorrhages and bright, white spots close to the macula in most patients with Bright's disease ("neuroretinitis albuminurica"). Koyanagi (1928) [161] likewise described white spots in nephritic retinopathy. Schieck (1930) [269] often observed bright, chalk-white spots, located close to the optic disc and vessels covering the macular area in albuminuric retinopathy. Schieck had already no-

ticed that the spots can disappear with only minor functional deficits. H. Friedenwald (1931) [84] noticed hemorrhages and white spots of various kinds which were usually scattered widely throughout the fundus, usually in advanced patients with hypertensive retinopathy.

Schürmann & MacMahon (1933) [289] described white patches, hemorrhages, papilledema, and narrow arteries with increased arterial reflexes and local narrowing in patients with albuminuric retinitis.

Kyrieleis (1939) [170] also found that gray-white CWSs in the inner retinal layer can develop rapidly during nephritis or eclampsia episode, often with extreme narrowing of adjacent vessels, and nerve-fiber degeneration. Evans & Stewart (1942) [77] described hemorrhages and fresh CWSs in the temporal retinal area and close to the optic disc in a 14-year-old girl with a pheochromocytoma. Rodin (1945) [260] observed retinal changes with numerous white patches around the macular region, principally of the "soft, fluffy, cotton wool type" in a patient with pheochromocytoma.

Scheie (1953) [266] found localized retinal degeneration. He assumed that ganglioform degeneration, or possible accumulations of fibrin in acute phases of severe hypertension resembled fluffy CWSs. Dollery & Hill (1961) [67] observed that CWSs reveal a definite cycle of changes. In the beginning, a faint, white haze occurs, then, they grow larger and denser over several days. They may disappear in a few days to eight weeks. Without any treatment for hypertension, CWSs may appear, grow, and resolve. They observed on four occasions an expanding CWS that deflected a blood vessel, which returned to its original position once the lesion had disappeared. The authors emphasized that they only found a thrombosed arteriole in relation to a CWS once, although they had examined serial pictures of over a hundred.

Klien (1965) [152] described numerous CWSs and marked attenuation of the retinal arteries due to acute toxemia during pregnancy in a 34-year-old woman. The CWSs were either elongated or round. Some revealed a serrated margin.

Shakib & Ashton (1966) [295] reported that CWSs represent a focal reaction of injured axons of still-living cells in the inner retina.

Ashton (1972) [16] described CWSs as a focal sign of ischemia due to occlusion of the supplying arteriole. Koch et al. (1972) [155] observed distinct remission of hypertensive retinopathy with CWSs during permanent dialysis and after kidney transplantation. Taylor et al. (1981) [319] described infarction of the optic nerve head in children with accelerated hypertension: the blood pressure in one child was 270/180 mm Hg. The right fundus on admission showed optic disc swelling, CWSs, and venous dilatation. The changes were bilateral and symmetrical.

Chaîne & Kohner (1983) [47] found retinal hemorrhages, CWSs, and hard exudates in patients with accelerated hypertension and increased vascular permeability. Brown et al. (1985) [39] described fibrinoid necrosis with occlusion of precapillary arterioles in patients with systemic hypertension. These occlusions might cause CWSs. Klein et al. (1994) [151] characterized hypertensive retinopathy by retinal microaneu-

rysms, blot hemorrhages, hemorrhages and/or microaneurysms, CWSs, hard exudates, intraretinal microvascular abnormalities, venous beading, and new vessels. Taban et al. (2006) [317] described during the fourth plasmapheresis treatment, reduced binocular visual acuity in a 15-year-old girl with IgA nephropathy and hypertension. Her retina revealed bilateral CWSs and serous retinal detachments.



Fig. 8. Multiple CWSs in a 69-year-old woman with arterial hypertension (blood pressure 220/120 mm Hg).

Optic disc edema with cotton-wool spots

Wall (1995) [335] described bilateral disc edema and CWSs in the temporal arcades and peripapillary hemorrhages in a 43-year-old man with a history of systemic arterial hypertension. BP was well controlled during follow-up: the disc edema nearly resolved, and his visual acuity was restored.

Valsalva maneuver and CWSs

Kocak et al. (2003) [154] described unilateral retinal hemorrhages and CWSs in a 17-year-old man who presented with sudden visual loss after weight-lifting. Examination after three months revealed normal visual acuity and complete recovery of the retina. They assumed that a brief but severe rise in blood pressure during the Valsalva maneuver caused the short-term retinopathy.

CWSs of varying duration; diabetic versus hypertensive retinopathy

Kohner et al. (1969) [157] emphasized that CWSs in hypertensive patients disappeared in six to 12 weeks and capillary perfusion then returned. However, CWSs in diabetic patients persisted for much longer periods. Their mean half-life was 8.1 months in patients under 40 years of age and 17.2 months in those over age 40. In four of six patients studied, some of the original CWSs were still present 30 months after they were

first observed. It is known that diabetics always present widespread and severe capillary disease. Kohner et al. (1969) [157] observed new vessels developing at the site of previous CWSs in two patients.

Bek & Lund-Andersen (1991) [24] noted that, in eight eyes of diabetic patients, their CWS - and corresponding scotoma - had not resolved one year after the first examination. Mean blood pressure showed no significant difference between the patients whose lesions resolved within three months, and those whose lesions persisted longer.

13.5 CWSs in conjunction with hemorrhages

Wilbrand & Saenger (1909) [340] already stated that white retinal spots were associated with hemorrhages.

Dollery & Hodge (1963) [68] observed CWSs in a retinal area that had undergone fluorescence angiography prior to lesion development. Microaneurysms in the vicinity of the CWS were apparent in 13 out of 18 examinations. The "ring" appearance of aneurysms only occurred after the CWS had appeared.

They detected a strong topographical association between CWSs and hemorrhages, and both with microaneurysms; an association between hemorrhages and areas of microaneurysms unrelated to CWSs was also noticed.

Hodge & Dollery (1964) [122] examined how CWSs correlate with hemorrhage, finding that both frequently appeared close together in the same retinal areas. 47% of 513 CWSs were close to, or direct in contact with one or more hemorrhages. Dollery et al. (1966) [69] reported a close topographical relationship between CWSs and hemorrhages in human hypertensive retinopathy, which were often situated around the CWSs. In an embolized retina, however, almost all CWSs were entirely free of associated hemorrhage.

13.6 Microaneurysms and vascular changes

J. S. Friedenwald (1949) [86] studied numerous CWSs, demonstrating that many contained curiously-irregular capillaries with very wide lumens and an irregular angular course.

Kohner et al. (1969) [157], observed that multiple microaneurysms and small capillary closure preceded the CWS, which only appeared when the arteriole to the area was occluded. Matas (1977) [192] found that microaneurysms may be present at the edge of the CWSs, lying in the nerve-fiber layer near the main arterial vessels or their branches. Brown & Magargal (1988) [40] also reported frequent microaneurysms in conjunction with CWSs, particularly in fluorescein angiography.

13.7 Epiretinal membrane contraction

Blockage of axoplasmic flow caused by epiretinal membrane contraction

Arroyo & Irvine (1995) [7] examined four patients with epiretinal membranes associated with prominent areas of intraretinal whitening involving the center of the fovea. These white areas were associated with surprisingly great inner retinal distortion. The appearance of these intraretinal white lesions were consistent with CWSs caused by mechanical axonal-flow disruption. They argued that membrane contraction and resultant

nerve-fiber layer distortion might cause the axoplasmic flow to become blocked, thus leading to CWSs.

13.8 Anemia

CWSs in aplastic anemia

Mansour et al. (2000) [189] found CWSs in 38% of 18 patients with aplastic anemia. Nerve-fiber layer or pre-retinal hemorrhages occurred often (67%). The authors argued that CWSs appear when the hemoglobin level drops below 7.8g/100ml, hypothesizing that retinal endothelial cell integrity is jeopardized by ischemia in severe anemia.

CWSs due to thrombotic thrombocytopenic purpura

Patel et al. (2001) [234] reported on a 52-year-old woman presenting bilateral diffuse retinal edema and whitening with confluent CWSs, mainly in the peripapillary area, and attenuation of the retinal arterioles, scattered hemorrhages, and a cherry-red spot due to thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

Power et al. (1997) [246] described peripapillary CWSs, intraretinal hemorrhages, venous engorgement, and macular whitening in a 29-year-old woman with thrombotic thrombocytopenic purpura. Fluorescein angiography revealed nearly confluent retinal capillary nonperfusion in the macula and peripapillary regions. The patient had microangiopathic hemolysis, and her hemoglobin had fallen to 0.1g/l. She suffered from thrombocytopenia and renal failure. After treatment, the CWSs and hemorrhages resolved.

Gum et al. (1988) [105] described sudden, massive bilateral capillary closure with severe visual loss in an anemic and diabetic 18-year-old woman, secondary to thrombotic thrombocytopenic purpura. The retina revealed confluent CWSs in both eyes. Despite treatment of the systemic diseases, her visual acuity remained impaired.

Different kinds of anemia

Merin & Freund (1968) [210] reported on retinopathy with CWSs due to severe anemia in patients with hookworm, cirrhosis, leukemia, and post-malaria disease. Holt & Gordon-Smith (1969) [127] noted retinal abnormalities in various diseases of the blood: acute leukemia, myelosclerosis, aplastic anemia, hemolytic anemia, multiple myeloma, pernicious anemia, and iron deficiency anemia. CWSs were seen in 14 patients with severe anemia whose hemoglobin level was under 6.6g. per 100 ml. in all but one; the mean hemoglobin concentration was 5.6 g. per 100 ml.

Iron deficiency anemia

Biousse et al. (2003) [30] reported on six patients (five women and one man) with iron-deficiency anemia and papilledema due to idiopathic intracranial hypertension. Two patients revealed CWSs. Their symptoms and signs improved dramatically after treatment of the anemia. Trujillo et al. (1972) [323] noted peripapillary white spots and retinal hemorrhages in a 37-year-old woman with papilledema in iron-deficiency anemia due to vaginal blood loss following a spontaneous abortion. Laibovitz (1982) [171] observed reversible bilateral AION in severe iron deficiency anemia in a

46-year-old woman; a single CWS was noted in the left eye.

Anemia due to blood loss

Retinopathy with CWSs due to massive blood loss was described by Horstmann (1878) [128], Ulrich (1887) [327], Pick (1901) [237], Pagenstecher (1905) [231], Pines (1931) [241], Pears & Pickering (1960) [235], Ashton et al. (1961) [11], Pickering (1969) [238], Hayreh (1987) [116], Schmidt & Neumann (2001) [279].

Severe blood loss occurred after miscarriage (Horstmann, 1878 [128], Pines, 1931 [241]), quinine and chloral-poisoning (Ulrich, 1887) [327], stomach cancer (Pick, 1901) [237], after duodenal ulcer (Pears & Pickering, 1960 [235], Pickering, 1969) [238], after peptic ulcer (Pagenstecher, 1905 [231], after gastrectomy (Hayreh, 1987) [116], gastritis, and heavy doses of aspirin (Schmidt & Neumann, 2001) [279]. Levatin (1947)[177] observed a hazy superior margin of the optic disc with a pale upper half in a 34-year-old man. A patch of "white substance" lay above the superior temporal vein.

13.9 CWSs and immunological diseases

Collagen diseases

CWSs have been described in patients with lupus erythematosus (LE), scleroderma, polyarteritis, dermatomyositis and other rheumatic diseases. Systemic LE is associated with occlusive retinal arteriolar disease possibly caused by the deposition of immune complexes in arteriolar walls.



Fig. 9. RE: Multiple CWSs in a 53-year-old woman with scleroderma.

Lupus erythematosus (LE)

Bergmeister (1929) [26] described retinal lesions in a patient with LE. He observed along the veins close to the papilla, white spots resembling cotton-wool measuring a quarter diameter of the papilla.

Disseminated lupus erythematosus (SLE) has been classified as a "collagen disease", along with rheumatic fever, rheumatic arthritis, periarteritis nodosa, generalized scleroderma, and dermatomyositis. This classification is a purely morphologic one, with no pathogenic significance. "Collagen disease" does not imply that these conditions have a common etiology.

A 26-year-old woman with SLE revealed several retinal white spots which appeared and disappeared in 35 days, while others had a cycle lasting as long as 81 days. Histological examination showed zones of hypertrophy of the nerve-fiber layers with zones of conglomerations of cytooid bodies between the nerve-fibers corresponding to the white spots (Brihayevan Geertruyden et al. 1954) [36]. Clifton & Greer (1955) [55] found circumscribed edema, venous congestion, and CWSs with retinal hemorrhages due to acute SLE in a 24-year-old woman. After ACTH therapy, the large white patches became smaller.

SLE is the prototype for circulating immune complex disease. Immune complex deposition results in an activation of the complement cascade with subsequent vasculitis (Terhorst et al. 1983) [321]. Fluorescein angiography in a 42-year-old woman demonstrated the obliteration of all retinal vessels except for major arteries and veins (Wong et al. 1981) [345]. Retinal vascular manifestation is the most common form of ophthalmic involvement in patients with SLE. They most frequently consist of CWSs with or without retinal hemorrhages (Koch et al. 1992) [156]. Fundus changes in patients with SLE can be quite variable. The most common changes are CWSs and infarcts in the nerve-fiber layer caused by inflammation of the small vessels. Although frequently referred to as arteritis or vasculitis, there are usually no other clinical signs of inflammation present in these eyes (Hall et al. (1984) [108]. Severe retinal vaso-occlusive disease and CWSs in eleven patients with SLE were published by Jabs et al. (1986) [131]. Jost et al. (1988) [134] reported on an anterior-segment ischemic syndrome shortly after pan-retinal photocoagulation in a 44-year-old woman with SLE. Retinopathologic progression with further arteriolar attenuation and increased CWSs were observed during follow-up.

Spencer (1996) [307] reported that microinfarctions of the nerve-fiber layer in the posterior pole as the main ocular finding in SLE. Thickening of the precapillary retinal arterioles bordering on CWSs was described. Montehermoso et al. (1999) [216] described a retinal vascular disease in 13 (15%) of 82 SLE patients. The retinopathy consisted in vascular occlusions in six patients, CWSs in three, papilledema in three, retinal hemorrhages in three, and AION in one patient. Antiphospholipid antibodies were detected in 10 (77%) of the 13 patients with retinal vascular disease due to SLE.

In SLE, CWS are scattered throughout the retina, and deep and superficial hemorrhages are often noticed. Several authors described the importance of retinal CWS in patients with SLE: Kurz (1938) [167], Klauder & Van Ellis (1939) [149], Maumenee (1940) [195], Gold et al. (1977) [98], Wong et al. (1981) [345], Kayazawa & Honda (1981) [137], Terhorst et al.

(1983) [321], Hall et al. (1984) [108], Jabs et al. (1986) [131], Klinkhoff et al. (1986) [153], Jost et al. (1988) [134], Drosos et al. (1989) [71], Koch et al. (1992) [156], Spencer (1996) [307], and Sellami (2002) [291].

Dermatomyositis and scleroderma

Klien (1965) [152] described retinal findings in a 17-year-old girl with dermatomyositis who revealed distinct retinopathy composed almost exclusively of partly single, partly confluent CWSs. In a 42-year-old woman with scleroderma of 7 years' duration and acute malignant hypertension, fulminant retinopathy was characterized by many CWSs. Besides the acute manifestation of CWSs in one eye, she observed a variety of vascular alterations causing scattered, small ischemic infarcts in all of the vascularized retinal layers, and fibrinoid changes in the vascular walls. Several foci containing cytooid bodies were noticed in the nerve-fiber layer. Munro (1959) [219] emphasized how the fundus lesions of dermatomyositis closely resemble those of SLE. In a 10-year-old boy with dermatomyositis, massive CWSs in both eyes, mainly scattered around the discs, were entirely confined to the posterior poles.

Pollack & Becker (1962) [243] found scattered lesions resembling CWSs of various sizes and shapes in the retina of a 65-year-old man with scleroderma. The largest CWS was about one-third of the disc size. CWSs were found in the proximity of retinal vessels. Histologic examination of the retinal changes revealed an accumulation of cytooid bodies.

Bone marrow transplantation (BMT)

Retinopathy with CWSs due to chronic graft-versus-host disease (GvHD) after bone marrow transplantation (BMT) were reported by Gratwohl et al. (1983) [102], Binaghi et al. (1983) [28], Gloor et al. (1985) [95], Pillunat et al. (1987) [240], Coskuncan et al. (1994) [59], Khawly et al. (1996) [138], and Ebner et al. (2001) [73].

BMT was necessary because of exacerbated acute leukemia (Binaghi 1983 [28], Gratwohl et al. 1983 [102], Gloor et al. 1985 [95], Pillunat et al. 1987) [240]. Coskuncan et al. (1994) [59], reported on seven patients with chronic myelogenous leukemia, three with acute lymphocytic leukemia and four with lymphoma. Ebner et al. (2001) [73] described the history of an 18-year-old woman with chronic myelogenous leukemia. Khawly et al. (1996) [138] observed five patients with breast cancer who developed retinopathy or optic neuropathy after BMT.

Time delay of visual loss due to GvHD after BMT

Visual deterioration usually occurred long after BMT: after ≤ 12 months (Binaghi et al. 1983) [28], three months (Gratwohl et al. 1983) [102], six months (Gloor et al. 1985) [95], and 17 months (Pillunat et al. (1987) [240]. Visual disturbances were noticed within 150 days after BMT (range 19 to 360 days) in 14 patients (Coskuncan et al. 1994) [59], and in one to five months in five patients (Khawly et al. 1996) [138]. Ebner et al. (2001) [73] reported GvHD on day 43, but visual loss not before day 126.

CWSs in giant cell arteritis (GCA)

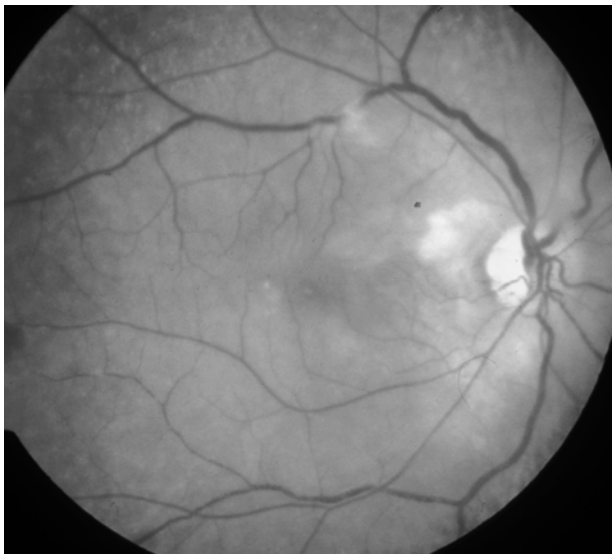


Fig. 10. RE: CWSs in a 89-year-old woman with GCA.

CWSs were described in GCA in several patients by: Andrews (1966) [4], Brégeat et al (1968) [34], Cohen & Damaske (1975) [56], Calamia & Hunder (1980) [44], Hamard et al. (1968) [109], Hines & Jones (1983) [119], Kilbourne & Wolff (1946) [140], Kimmerling & Nordin (1952) [142], Kreibig (1953) [165], Lessell et al. (1977) [176], MacLeod & Rizk (1993) [184], McLeod et al. (1978) [204], Melberg et al. (1995) [209], Modai et al. (1971) [215], Post & Sanders (1944) [245], Riu et al. (1966) [258], Schmidt (1995, 2003, 2005) [274, 281, 285], Thystrup et al. (1994) [322], Velusami et al. (2006) [330].

AION and CWSs

Currie & Lessell (1984) [62] described the symptoms of a 63-year-old woman who reported on a "bright flash of light". A slight flare and a few cells were observed in the aqueous humor bilaterally. The retina in one eye revealed CWSs. Fluorescein angiography disclosed swelling of one optic disc with leakage of dye from the vessels.

The cause of peripapillary CWSs may be focal retinal ischemia following arteritic occlusion in some pos-

Table 5. Amaurosis fugax as the first symptom in patients with CWSs (patients with GCA).

Cohen & Damaske (1975) [56]	A 63-year-old man complained of visual "blackouts" which lasted from 1/2 hour to 3 hours at a time. The swinging flash light test was normal bilaterally. On ophthalmoscopic examination the optic discs were normal but there were several CWSs in the left retina.
Calamia & Hunder (1980) [44]	16 of 100 patients with GCA experienced only transient impairment of vision. In only two of these patients was the ophthalmoscopic examination abnormal. In one patient with amaurosis fugax CWSs were seen.
Schmidt (1995, page 170) [274]	A 73-year-old woman noticed scintillations in the left eye. The only objective ocular finding was one CWS adjacent to the left optic disc. Visual acuity was normal.
Velusami et al. (2006) [330]	A 59-year-old male complained of transient bilateral visual blur for a few hours followed by complete resolution. Visual acuities in both eyes were normal. Fundus examination showed numerous elevated CWSs in both eyes with normal looking optic discs and maculae. Fluorescein angiography showed poor and reduced filling of the retinal circulation.

Table 6. Occurrence of CWSs in patients with GCA.

Andrews (1966) [4]	A 67-year-old woman who was totally blind revealed CWSs associated with a few linear hemorrhages near the optic discs.
McLeod et al. (1978) [204]	In a 75-year-old woman vision in each eye was reduced to perception of hand movements. Both eyes revealed pale swellings of the optic discs and CWSs. Fluorescein angiography of the left eye showed markedly impaired perfusion of retinal and ciliary arteries. In the left eye wedge-shaped areas of pigment epithelial disturbances were noted. Bands of pigmentary change (Siegrist steaks) were also present.
Thystrup et al. (1994) [322]	Fundus examination revealed an ischemic optic disc in a 66-year-old woman. Visual acuity in the right eye was distinctly reduced. Visual acuity in the left eye was normal. CWSs adjacent to retinal venules were present in both fundi.
Melberg et al. (1995) [209]	Seven patients (age: 58-79 years) with GCA showed CWSs prior to visual loss. No afferent pupillary defect was present in these patients.
Schmidt (1995, page 128) [274]	A 75-year-old man complained about amaurosis fugax in both eyes. In the left eye a CRAO occurred with CWSs adjacent to the optic disc.

Table 6 continued.

Fineman et al. (1996) [79]	A 77-year-old woman revealed a hemiretinal artery occlusion in the left eye with associated CWSs.
Hayreh et al. (1998) [118]	One third of the eyes with visual loss (83 patients) had CWSs at the posterior pole during early stages of the disease.
Daudin et al. (2006) [63]	A 63-year-old man noticed a mild visual loss in the right eye. Ophthalmoscopy revealed unilateral several CWSs. Fluorescein angiography showed a prolonged arterio-venous transit time. Prompt treatment with corticosteroids led to resolution of CWSs.

terior ciliary arteries, cilioretinal arteries, or retinal arterioles.

McLeod & Kohner (1977) [203] stressed that peripapillary CWSs resulted from partial occlusion of the extraocular course of the central retinal artery in GCA. In cases of partial central retinal artery occlusion (CRAO), the white axoplasmic debris accumulates at the border between ischemic and nonischemic retina in the peripapillary region. The authors emphasized that CWSs do not represent microinfarcts.

McLeod et al. (1978) [204] reported on a 75-year-old woman with GCA who revealed pallor and swelling of the optic disc, and CWSs in the nerve-fiber layer. CWSs delineated ischemic retina in both eyes, which was attributed to obstruction of orthograde axoplasmic transport.

A 73-year-old woman with the characteristic signs and symptoms of biopsy-proven GCA complained about scintillation in her left eye. That eye's retina revealed one CWS temporal and adjacent to the optic disc. Visual acuity and visual field were normal (Schmidt 1995) [274].

Selsky & Nirankari (1985) [292] reported on a 66-year-old woman who developed complete blindness in both eyes due to GCA. The retinal examination showed one CWS in her right eye, but no other abnormalities in the fundus.

MacLeod & Rizk (1993) [184] described CWSs in a 69-year-old woman with GCA. CWSs were found adjacent to the normal-appearing optic disc, and visual acuity was normal. Melberg et al. (1995) [209] reported on seven patients (age: 58-79 years) with GCA, stressing that CWSs are an early ophthalmoscopic finding in GCA and can precede severe visual loss. No afferent pupillary defect was present in these patients. Although CWSs were a prominent early finding in their patients, they probably also had subclinical optic nerve ischemia. Four patients demonstrated late hyperfluorescence of one or both normal-appearing optic nerve heads. McLeod & Kohner (1996) [206] emphasized that peripapillary CWSs could be a consequence of extraocular arteritic occlusion involving the posterior ciliary arteries and cilioretinal circulation, or the arterial supply to the inner retina with obstruction of axoplasmic flow. Schmidt (2003) [281] reported that amaurosis fugax is not a rare symptom in GCA. CWSs can sometimes be found after a such a sudden transient visual disturbance.

Schmidt (1996) [275] observed one small CWS superior to the optic disc due to GCA in a 75-year-old

woman with bilateral AION and small peripapillary hemorrhages.

Schmidt & Vaith (2005) [284] reported on an 80-year-old woman with bilateral blindness due to GCA. The right eye showed papilledema and peripapillary CWSs. Schmidt (2005) [284] observed an ocular ischemia syndrome due to GCA in an 84-year-old woman. The retina revealed several CWSs in both eyes. Eye pressure decreased to 2 mm Hg in the right and 4 mm Hg in the left eye. CWSs should alert clinicians to a potentially malignant GCA outcome. Velusami et al. (2006) described CWSs in both eyes of a 58-year-old man with occult GCA. He complained about bilateral visual blur lasting a few hours. The eye examination revealed normal visual acuity and normal-appearing optic discs and maculae. While awaiting the biopsy results, additional examination showed visual loss in his right eye to counting fingers. His vision improved on high-dose steroids, with some constriction of peripheral visual field. Daudin et al. (2006) described unilateral multiple CWSs in a 63-year-old man with GCA as the only ocular sign without a drop in visual acuity. The patient had noticed blurred vision for two days before examination. The CWSs resolved after corticosteroid treatment.

Fineman et al. (1996) [79] described a hemiretinal artery occlusion involving the superior half of the macula and CWSs adjacent to the retinal edema in a 77-year-old woman with GCA. After megadose of methylprednisone, retinopathy resolved. Visual acuity stabilized at hand motions.

Behçet's disease

Dominguez & Irvine (1997) [70] reported that posterior uveitis due to Behçet's disease can be extremely variable, including optic neuritis, retinal vasculitis, and small white patches of retinitis. Small white patches of retinitis were the most common, and often first signs of recurrent activity. The presence of small patches of retinal whitening is the most characteristic finding in Behçet's disease. Some of the white patches around the left optic nerve resemble CWSs. The patches of retinitis varied from grayish lesions seeming to lie in the outer retina, to intense white lesions appearing to involve all retinal layers. Those lesions were different from CWSs.

Takayasu's arteritis

Karam et al. (1999) [136] reported on eight patients with Takayasu's arteritis. Unusual findings included CWSs, AION and retinal emboli.

Wegener's granulomatosis

Bullen et al. (1983) [42] found retinal disease in seven of 140 patients with biopsy-proven Wegener's granulomatosis. Retinal hemorrhages, edema, and CWSs were observed in four patients.

CWSs as the initial ocular manifestation in Wegener's granulomatosis

Mangouritsas & Ulbig (1994) [187] detected bilateral CWSs as an initial ocular manifestation of Wegener's granulomatosis. Their findings were highly unusual, and were interpreted as a possible focal retinal inflammatory vasculitis.

Spalton et al. (1981) [306] described a swollen right optic disc and focal periphlebitis in the temporal retina in a 12-year-old boy with Wegener's granulomatosis. The focal periphlebitis resembled CWSs.

CWSs in patients with sarcoidosis

Prost (1999) [249] reported on three patients with unilateral CWSs of initially unknown etiology in whom the diagnosis sarcoidosis was made six to 16 months later. The suspected diagnosis sarcoidosis was confirmed by bronchoscopic and conjunctival biopsies. The serum angiotensin converting enzyme was elevated in one patient. After corticosteroid treatment the CWSs resolved.

Panarteritis (Polyarteritis) nodosa (PAN)

Friedenwald & Rones (1931) [85] noted numerous bilateral hemorrhages and CWSs and retinal edema, as well as marked arteriosclerosis in a 55-year-old man with PAN. Histology revealed serous exudates with cytoid bodies and areas of infiltration with fat droplet cells similar to findings in albuminuric retinitis. Walsh and Hoyt (1969) [336] described retinal hemorrhages, edema, CWSs, and CRAO in patients with PAN. The retinopathy of PAN can occur secondary to coexistent hypertension, but also due to retinal vasculitis. Binaghi et al. (1984) [29] reported on a 37-year-old man and 34-year-old woman with CWSs and sporadic retinal hemorrhages due to PAN.

Schmidt et al. (2001) [278] described a CRAO with multiple CWSs in a hypertensive 67-year-old man with PAN.

CWSs and microscopic polyangiitis

Mihara et al. (2004) [212] observed a hypopyon iridocyclitis in the right eye and CWSs in the left eye due to microscopic polyangiitis in an 83-year-old woman. White blood cell count and P-ANCA titer were elevated. Skin biopsy revealed necrotizing inflammation of small vessels. After treatment with systemic and topical corticosteroids, ocular symptoms improved in both eyes.

Antiphospholipid syndrome

The eye is frequently involved in primary antiphospholipid syndrome.

Castanon et al. (1995) [45] reported on fundus abnormalities in 15 of 17 patients with primary antiphospholipid syndrome. Disc edema, vitreous hemorrhages, CWSs, vitreous bands, serous macular de-

tachment of the macula and capillary abnormalities were described. Vaso-occlusive retinopathy in six eyes were verified by fluorescein angiography.

Cryoglobulinemia

Myers et al. (2001) [220] observed peripapillary CWSs and superficial retinal whitening in the macula in a 44-year-old man with chronic hepatitis C who developed abdominal pain and sudden visual loss in the left eye. Markedly elevated rheumatoid factor, hypertension, and acute kidney failure were diagnosed. Renal biopsy revealed intravascular deposition of immunoglobulins IgG and IgM and complement consistent with type-II mixed cryoglobulinemia. Complement-mediated microemboli have been assumed to co-exist with leukoemboli and immune complexes causing vaso-occlusion in mixed cryoglobulinemia.

Thromboangiitis obliterans

Gresser (1932) [104] described distributed white, "fluffy areas of degeneration" and papilledema with fairly large retinal hemorrhages in a 56-year-old male with thromboangiitis obliterans.

Polycythemia

Hyperviscosity may lead to venous thrombosis with engorged retinal veins and hemorrhages in patients with polycythemia. A CRAO was also observed. Lisch (1940) [180] described a CWS as opaque retinal swelling adjacent to an arteriole in a 41-year-old woman with polycythemia.

Retinopathy due to progressive systemic sclerosis (PSS)

Ashton et al. (1968b) [15] noticed a retinopathy, characterised by CWSs containing cytoid bodies, neuroretinal and optic nerve-head edema, sero-fibrinous exudates, and capillary hemorrhages as signs of ischemic vascular damage resulting from fibrinoid change in the pre-capillary arterioles of both retina and choroid in a 64-year-old woman suffering from PSS and hypertension (230/110 mm Hg). The key role played by retinal changes was attributed to vascular involvement by PSS.

*13.10 Arterial occlusion**CWSs and central retinal artery occlusion (CRAO)*

Oji & McLeod (1978) [227] reported on multiple circumpapillary CWSs and mild ischemic swelling of the inner retina in a patient with partial CRAO. The CWSs formed a "circinate" configuration. Most of the CWSs delineated the border between normal parapapillary retina and the more peripheral retina, which showed mild ischemic swelling.

Ong et al. (2002) [228] described a retinopathy with a pale swollen disc associated with CWSs and moderately-engorged retinal veins in a 69-year-old man with inferior field loss in one eye. Fluorescein angiography revealed a delayed choroidal filling. A proximal ophthalmic artery stenosis was detected by computed tomography angiography. Ophthalmic artery hypoperfusion was diagnosed. The retinopathy improved and CWSs disappeared in the following months.

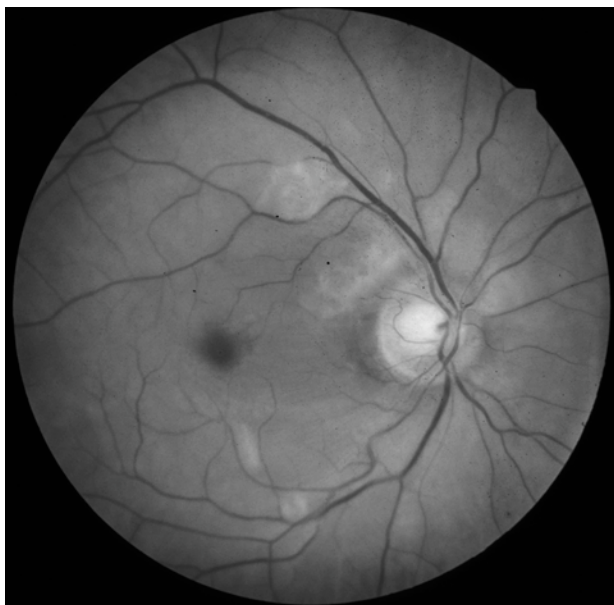


Fig. 11. RE: Central retinal artery occlusion with CWSs in arterial hypertension (blood pressure 215/140 mm Hg) in a 51-year-old male.

Amaurosis fugax and CWSs in patients with central retinal artery occlusion

Schmidt et al. (1992) [272] observed a large CWS just under the optic disc, as well as many tiny CWSs surrounding the papilla and in the region of the great vascular arches. Central retinal edema was present, along with a cherry-red macula in the 69-year-old woman who had noticed a sudden reduction in vision in her left eye due to CRAO. She had experienced an earlier attack of amaurosis fugax lasting about ten minutes.

Schmidt (2004) [283] described two 48- and 70-year-old patients with sudden visual loss due to an incomplete CRAO. Both showed multiple CWSs in the posterior pole of the affected eye, demonstrating that CWSs can already occur during an attack of amaurosis fugax.

CWSs and small vessel disease

CWSs have been observed in systemic diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL disease). Cumurciuc et al. (2004) [61] noted CWSs in three patients with CADASIL disease.

Sickle-cell hemoglobinopathies

Asdourian et al. (1976) [8] described CWSs in the right posterior pole with one of the patches extending to the superior border of the fovea in a 26-year-old woman with sickle cell-hemoglobin C disease.

Jampol & Rabb (1981) [133] highlighted retinal ischemia in patients with areas of capillary nonperfusion with CWSs in the acute phase of the disease. Precapillary arterioles were obstructed by sickle-shaped erythrocytes. The foveal avascular zone may be enlarged and irregular. Changes in the posterior pole also closely resemble those of hypertensive retinopathy.

13.11 Stenosis or occlusion of the internal carotid artery (ICA)

Ischemic oculopathy due to ICA occlusion

Schenk (1955) [267] reported on about 30 CWSs located partially in front or adjacent to retinal vessels in a 24-year-old woman after ligation of the carotid artery. The spots resolved after two to three weeks. Makabe (1974) [186] noted stenoses of the internal carotid arteries (ICAs) in three patients. Ipsilateral eye pressure was reduced. All patients revealed retinal hemorrhages and CWSs.

Cowan & Butler (1983) [60] observed several small nerve-fiber layer infarcts with CWSs in a 58-year-old woman with unilateral visual loss. Anterior uveitis, rubeosis, and glaucoma were also observed due to complete occlusion of the ICA on the same side.

A 67-year-old man with bilateral ICA occlusions showed iris neovascularization and a flare in the anterior chamber (Jungmann et al. 1987) [135]. The retina revealed narrow arteries, CWSs, and hemorrhages, and there were several striking ghost vessels in the retinal periphery.

Schönherr et al. (1990) [287] described internal carotid kinking revealed in digital subtraction angiography in a 57- and in a 74-year-old patient. In one, a recurrent anterior ischemic optic neuropathy (AION) and some peripapillary CWSs occurred, and in the other, CWSs were also found in the retina. The area surrounding the kinked artery was surgically removed, as it was considered to be at risk of embolism.

Morales et al. (2002) [217] reported on a 42-year-old man with a high-grade stenosis in the innominate, and left common carotid arteries. The patient complained of worsening vision. The retinal arteries were attenuated, and CWSs were observed in both fundi.

Intraretinal gray lesions as a sign of reversible visual loss following prolonged ophthalmic artery hypoperfusion

Cherny et al. (1991) [50] described ocular ischemia with CWSs and deep gray intraretinal lesions in a 49-year-old woman who had developed severe unilateral visual loss following carotid artery balloon occlusion for a carotid cavernous fistula. Visual acuity was restored by subsequent balloon occlusion of the ophthalmic artery, despite profound visual loss and ocular ischemia.

Temporary loss of vision after postsurgical hypotension

Sharma & Sharma (1976) [297] observed ischemic retinas with a few CWSs and deep hemorrhages and an acute visual impairment in a 50-year-old woman who experienced a drop in systolic blood pressure from 94 to 84 and later 72 mm Hg following head trauma.

13.12 Cardiac disease

Kozłowski & Peters (1992) [164] reported on a previously-healthy 30-year-old man who lost consciousness for no apparent reason. On awaking he noted bilateral visual loss. Fundus examination revealed multiple superficial peripapillary and macular patches of retinal whitening and hemorrhages. A chest X-ray showed a calcified mass caused by an aneurysm communicating with the left ventricle. A left occipital infarct was diagnosed by CT examination, and the aneurysm successfully excised.

Complications during coronary intervention

Kusano et al. (2003) [168] noticed bilateral peripapillary CWSs with retinal microangiopathy following percutaneous transluminal coronary angioplasty and stent insertion for acute myocardial infarction in seven patients. The lesions resolved spontaneously within several months. The authors assumed that the retinopathy developed after microembolization from the atherosclerotic arteries. Kinoshita et al. (2004) [145] observed peripapillary CWSs in 17 of 30 patients (57%) after percutaneous coronary interventions (PCI) after acute myocardial infarction (AMI). Fluorescein angiography in three patients showed non-perfused areas around the CWSs.

13.13 Retinal vein obstruction

Prognosis for rubeosis iridis following central retinal vein occlusion (CRVO)

Sinclair et al. (1979) [300] reviewed the records of 57 patients with recent CRVO in order to predict the development of rubeosis iridis (RI) and neovascular glaucoma (NVG).

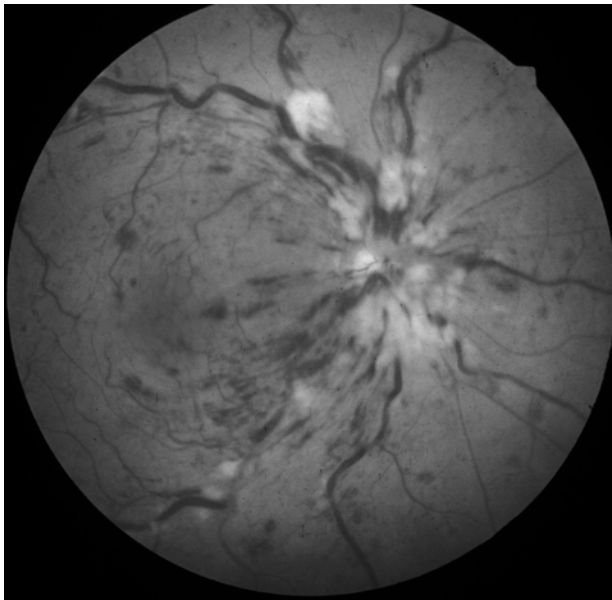


Fig. 12. RE: CWSs in a 50-year-old male with central vein occlusion papilledema, hemorrhages, CWSs due to arterial hypertension.

Severe retinal ischemia occurred in 12 patients (21%) who developed RI and NVG, and this complication appeared to correlate most significantly with clinical and fluoroangiographic findings. Among patients with over 10 CWSs, RI developed in 75%, whereas the incidence was 24% in patients in whom fewer than 10 CWSs were observed, and only 14% if none were identified ($p \leq 0.001$).

CMV retinitis with disc CWSs (without HIV infection)

Schmidt & Hörl (1990) [271] reported on a unilateral inflammatory cause of CRVO, two years after kidney transplantation in a 47-year-old man who was treated with immunosuppressive agents. High titers of cy-

tomegalovirus (CMV) were observed when the vein occlusion was diagnosed. The optic disc revealed whitish CWSs caused by ischemia. There was an association between the CMV infection and vein occlusion: once the CMV was treated, visual function improved. The patient was not HIV-positive.

Presence of CWSs not predictive in progressive vein occlusion

Minturn & Brown (1986) [214] examined 16 patients with CRVO who presented with nonischemic CRVO that progressed to an ischemic CRVO. This subgroup was compared to a control group of 34 patients with a nonischemic CRVO did not progressing to the ischemic state. By analyzing the initial and last fundus photographs no difference was found between the two groups in the presence of CWSs, venous sheathing, optociliary shunt vessels, or degree of hard exudates.

Correlation between aqueous flare values and number of CWSs

Nguyen & Kuchle (1993) [225] used the laser flare cell meter to evaluate alterations in the blood-aqueous barrier in eyes with retinal vein occlusion (RVO). In 42 eyes with RVO, aqueous flare and aqueous cells were determined and compared to those of normal control eyes. Flare values in the CRV eyes were significantly higher than in eyes with branch retinal vein occlusion (BRVO). Significant correlations were found between flare values and the RVO area and between flare values and retinal non-perfusion area. One important finding was the significant correlations between flare values and number of CWSs, and between cell counts and degree of cystoid macular edema.

Several reports on CWSs in patients with retinal vein occlusion

Archer (1976) [5] described extensive hemorrhages and CWSs due to a branch retinal vein obstruction in a 66-year-old male.

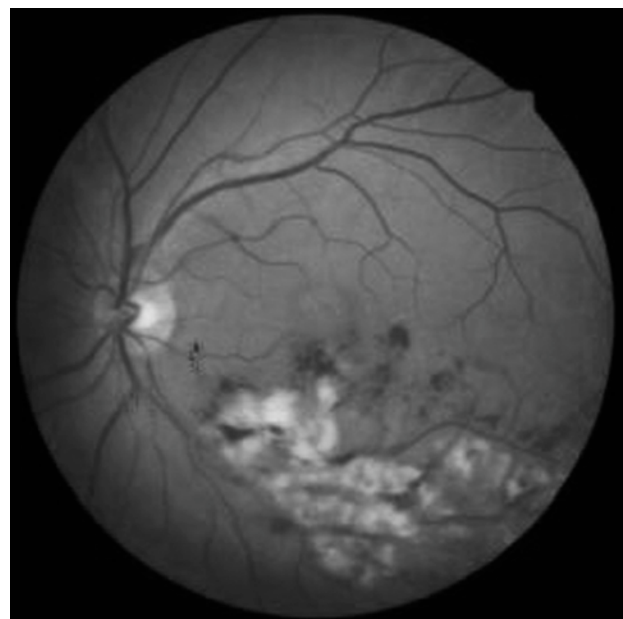


Fig. 13. LE: Branch retinal vein occlusion with multiple CWSs in the area of the inferior temporal vein in a 30-year-old woman who was treated with contraceptive drugs.

Hayreh (1983) [114] found a few small patches of retinal capillary obliteration in areas of CWSs with multiple scattered retinal hemorrhages and macular edema as signs of a central retinal vein occlusion (CRVO) in a 56-year-old man.

With arterial hypertension, extensive CWSs with only moderate numbers of retinal hemorrhages as signs of a venous occlusion were described in a 38-year-old male. Dithmar et al. (1997) [65] noted avascular areas by angiography in a 74-year-old man who presented extensive retinal hemorrhages and CWSs indicating a CRVO. Retinal neovascularizations were also observed as signs of retinal ischemia. Kottow & Metzler (1975) [160] found engorged and tortuous retinal veins. The posterior pole was covered with large blot hemorrhages, macular edema, and CWSs in a 66-year-old male. Morse (1985) [218] observed along an area of retinal edema, CWSs and hemorrhages the course of the inferotemporal vascular arcades as signs of venous occlusion in a 63-year-old woman. Stoffelns et al. (2007) [311] described an ischemic CRVO with CWSs, distinct swelling of the optic disc, and dark hemorrhages in a 54-year-old. He was successfully treated with radial optic neurotomy.

13.14 Infectious diseases

Acquired immunodeficiency syndrome (Aids)

CWSs should alert the clinician to suspect Aids

Rosenberg et al. (1983) [262] emphasized that asymptomatic patients undergoing routine ophthalmic evaluation presenting CWSs without discernible cause should alert the clinician to suspect Aids. Nine of the 18 patients with Aids had CWSs. Fluorescein angiography showed typical areas of retinal capillary nonperfusion.

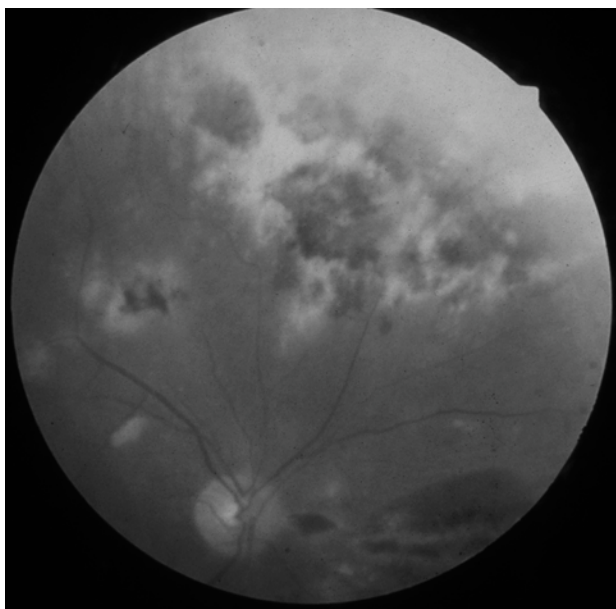


Fig. 14. Retinal changes of a 42-year-old man with cytomegalovirus (CMV) retinitis associated with CWSs.

CWSs as the most common ocular manifestation of Aids

Holland et al. (1983) [125] found CWSs in 16 of 30 Aids patients as the most frequent ocular finding. All

those with CWSs had cytomegalovirus retinitis (CMV) infection. A strong correlation between CWSs and multiple opportunistic infections was noted.

Brown et al. (1985) [39] also stressed that the most common ocular manifestation of Aids is the presence of CWSs, which occur in about 50% of patients. Most of these patients contract opportunistic infections such as candida albicans, pneumocystis carinii, toxoplasma gondii, or CMV. Brezin et al. (1990) [35] reported on nine of 29 patients (31%) with Aids-Related Complex (ARC). Patients with CWSs had a poorer prognosis than those without CWSs. Leukocyte counts were found to be significantly lower, and the proportion of patients with significant weight loss was greater among ARC patients with CWSs. Among the nine patients with CWSs during follow-up observation, seven developed major opportunistic infections or HIV-related neoplasias. Pepose et al. (1985) [236] described ocular findings in 35 Aids patients. Light and electron microscopic studies from the eyes revealed CWSs (71 % of cases), retinal hemorrhages in areas without CMV infection (40%), CMV retinitis (34%), Roth's spots (23%), retinal microaneurysms (20%), and papilledema (14%). Ultrastructural studies showed vasculopathy around the CWSs. The authors did not detect CMV antigens or inclusions in any retinal vascular endothelium, concluding that the virus infects the retina via breaks in the blood-ocular barrier rather than via endothelial cell infection in Aids patients.

Pomerantz et al. (1987) [244] noted yellow-white necroses and hemorrhages in the superior portion of the left retina in a 32-year-old man (consistent with CMV retinitis) and multiple CWSs. The right retina showed multiple CWSs. It has been hypothesized that CWSs in the presence of HIV infection are caused by occlusion of retinal arterioles and capillaries as a result of immune-complex deposition.

Pivetti Pezzi et al. (1989) [242] emphasized that CWSs were the most common ocular manifestations in HIV-infected subjects. 58.8 % of Aids patients and in 76.9% of those with ocular involvement revealed CWSs. A close correlation between ocular changes and decrease of CD4+ lymphocytes was observed.

Schmitt-Gräff et al. (1990) [286] found severe unilateral cytomegalovirus (CMV) retinitis due to Aids in a 44-year-old man. The retina of the opposite eye was not involved by CMV but revealed CWSs. Histologically, areas of edematous nerve-fiber swelling were consistent with focal retinal ischemia in that eye.

CWSs reflect the patient's general condition

Newsome et al. (1984) [224] reported on 12 of 13 patients with Aids. Microvascular abnormalities frequently encircled some of the more dense CWSs. A depression sign detected in the red-free photographs of the posterior poles in some cases was considered as a loss of retinal tissue. Thus, CWSs appear to be the final common pathologic expression indicating the presence of focal ischemia at the level of the nerve-fiber layer. CWSs reflected the patient's general condition. In a few patients whose general condition had been stable, the numbers of CWSs had decreased. However, the number of CWSs rose in those patients

whose general condition had deteriorated with new and recurring infections including CMV retinitis.

Different opportunistic infections in Aids

Gonzalez et al. (1996) [99] found that 90% of CWSs were positive for CMV DNA versus 22% of peripheral retinal biopsies without CWSs. Retinal CWSs were associated with advancing HIV infection. As a strong association between CWSs and CMV has been identified, it has been hypothesized that CMV enters the retina via damaged microvasculature.

Regarding multiple CWSs in pneumocystis carinii infection due to Aids: Kwok et al. (1982) [169] found multiple CWSs in both eyes, distributed along the major temporal and nasal arterioles in a 34-year-old man with pneumocystis carinii infection. Microscopy of the eyes showed areas of nerve-fiber-layer degeneration and cytooid bodies. Electron-microscopy revealed the cystic form of pneumocystis carinii in the ganglia and inner plexiform layers of the retina in the vicinity of retinal vessels. Bach & Hedstrom (1987) [19] described multiple CWSs in a 39-year-old man with biopsy-proved toxoplasmosis and chronic candidiasis.

CWSs are significant predictors of CMV retinitis

Hodge et al. (2004) [123] noted that flashing lights or floaters, and CWSs are significant predictors of CMV retinitis. Areas of retinal microinfarction with capillary occlusion may lead to CMV entering the retinal tissue.

Ocular manifestations associated with low CD4+ counts

Spaide et al. (1995) [305] examined the possible risk factors in 453 male patients with a positive serodiagnosis for human immunodeficiency virus (HIV), finding that the ocular manifestations of HIV infection correlate with low CD4+ counts. Age was not a significant predictor of CWSs or CMV retinitis.

Predilection of CWSs for the temporal quadrants

Mansour et al. (1988) [188] noticed that CWSs had a predilection for the temporal quadrants in four diseases: Aids, diabetes mellitus, systemic hypertension, and central retinal vein occlusion (CRVO). However, CWSs were smaller in patients with Aids than in the other groups. Patients with ischemic CRVO had more CWSs than the other groups. In patients with Aids, the CWSs were predominantly located along the vascular arcades, with a strong predilection for the posterior pole. There was an average of 5.3 CWSs per fundus (range one to 24; SD 6.2). Microaneurysms had often formed on the CWS borders. There was an average of 5.5 CWSs per fundus in diabetics (range 1 to 21; SD 4.8). In patients with arterial hypertension, they noted an average of 3.4 CWSs (range, 1 to 10; SD 3.4), in those with CRVO, the average number of CWSs was 22.7 per eye (range 6 to 35; SD, 9.5). The largest CWSs were noted in CRVO patients.

Four major ocular categories in Aids

Palestine et al. (1984) [232] examined 40 patients with Aids examined for ocular abnormalities. 50% of the patients showed ocular signs attributable to Aids. Ocu-

lar findings were confined to four major categories: CMV retinitis (10 patients), retinal CWSs (11 patients), conjunctival Kaposi's sarcoma (two patients) and neuro-ophthalmologic motility abnormalities (three patients).

The CWSs regressed over a period of a few months. One patient had hemorrhages in addition to CWSs. Another had CWSs and CMV in the same eye. All patients in this study were mildly anemic, but their average hemoglobin levels were not significantly different from those without CWS lesions.

Unilateral CMV retinitis but bilateral CWSs

Rodrigues et al. (1983) [261] reported on a 42-year-old man with Aids, cryptococcal meningitis, disseminated mycobacterium avium-intracellulare with mycobacteremia and oropharyngeal candidiasis who developed unilateral retinitis and bilateral CWSs. Histopathologic examination revealed unilateral necrotizing retinochoroiditis with virions in retinal and choroidal tissues. Postmortem cultures of retina and choroid were positive for CMV.

In the right eye, multiple, fluffy retinal infiltrates were observed, many of which were associated with small hemorrhages. The retinal involvement was most marked temporal to the macula where there was a large confluent area of infiltrate. In the left eye, multiple small white retinal infiltrates without hemorrhages were observed, resembling CWSs. Electron-microscopy of CWSs showed only typical cytooid bodies with nucleoid structures, neurofilaments, mitochondria, and dense bodies.

Syphilis and Aids

McLeish et al. (1990) [198] reported on a 46-year-old man with syphilis and Aids. One eye revealed two CWSs, the other dense vitreous cellularity with a distinctly impaired visual acuity. Zambrano et al. (1987) [347] described bilateral syphilitic optic neuritis and numerous scattered CWSs in the right eye with no evidence of phlebitis or hemorrhages in a 23-year-old male with syphilis and Aids. His vision deteriorated from 20/20 to total bilateral blindness as a result of syphilitic retrobulbar neuritis.

Syphilis without Aids

Schmidt et al. (2002) [280] reported on eye symptoms in patients with syphilis. A 55-year-old man revealed papilledema and a CWS together with a hemi-central retinal vein occlusion.

CWSs in cat-scratch disease

Reed et al. (1998) [256] described ophthalmoscopic findings in seven patients with cat-scratch disease due to Bartonella henselae infection. The patients revealed neuroretinitis, including nerve-fiber hemorrhage, CWSs, multiple discrete lesions in the deep retina, and stellate macular exudates.

Pieh et al (2005) [239] found CWSs in a 16-year-old girl with visual deterioration. Both retinas showed two CWSs and slight retinal edema. The Bartonella henselae IgG-titer was slightly elevated and increased in control examination. The patient recovered after antibiotic treatment.

CWSs in Rocky Mountain spotted fever

CWSs were described in patients with Rocky Mountain spotted fever by Presley (1969) [248], Raab et al. (1969) [253], and Smith & Burton (1977) [303]. All patients also revealed bilateral optic disc swelling. The young patients had been bitten by a tick. Smith & Burton (1977) [303] found capillary nonperfusion and focal areas of intraretinal and perivascular staining in the fluorescein angiogram in a 9-year-old girl.

CWSs in leptospirosis

Gutman et al. (1983) [106] noted CWSs as signs in leptospirosis (Weil's disease) in a 44-year-old man who presented with fever, myalgia, and weakness. Ocular changes were subconjunctival hemorrhages and anterior uveitis. Fluorescein angiography revealed areas of retinal capillary nonperfusion corresponding to the CWSs. The leptospirosis antibody titers were raised. The patient was successfully treated with systemic steroids.

CWSs in Dengue fever

Siqueira et al. (2004) [301] described bilateral retinopathy with vascular sheathing, retinal hemorrhages, and CWSs in a 32-year-old woman suffering from blurred vision 13 days after an episode of Dengue fever, confirmed by positive IgM ELISA to the Dengue virus. In addition to the retinopathy, vitreous hemorrhage developed with preretinal neovascularization in one eye. Vitrectomy and panretinal photocoagulation were carried out, nevertheless, her visual acuity failed to improve.

CWSs after smallpox vaccination

Landa et al. (2006) [172] reported on a retinal infarct in conjunction with multiple CWSs on the posterior pole of the fundus. Multiple branch retinal arteriolar occlusions associated with smallpox vaccination were observed in one eye in a 53-year-old patient. He had received a smallpox vaccination on the day before he noticed a sudden temporal field loss. Magnetic resonance imaging (MRI) of the brain depicted white-matter focal lesions. He was successfully treated with methylprednisolone and immunoglobulins.

Retinal lesions in septicemia

Neudorfer et al. (1993) [223] examined retinal lesions in septicemia in order to identify the association between septicemia and specific retinal lesions in a prospective controlled study. Hemorrhages, CWSs, or Roth's spots were found in 24 of 101 septic patients, but only in four of 99 patients in the control group (4%). Histologic examination of affected eyes disclosed cytooid bodies in the nerve-fiber layer without inflammation.

Cerebral malaria and retinopathy

Children with cerebral malaria reveal the following fundus entities: hemorrhages (with and without white center), CWSs, papilledema, retinal whitening and vessel abnormalities. Hirneiß et al. (2005) [120] found CWSs in 22 of 439 children (5 %).

CWSs in hepatic cirrhosis

Dittmer et al. (1998) [66] described pathological reti-

nal findings in eleven patients with hepatocirrhosis. CWSs were found in five patients. Additional findings were: discrete vessel abnormalities in three patients, intraretinal hemorrhages in two, and papilledema in another patient. They concluded that these retinal abnormalities had developed due to reduced retinal perfusion. The retinal changes improved after a transjugular intrahepatic portosystemic stent surgery (TIPS).

13.15 CWSs in pancreatitis

Occluded macular retinal arterioles in retinopathy with CWSs and hemorrhages were observed in patients with acute pancreatitis by Cohen et al. (1989) [57] and Inkelles & Walsh (1975) [129]. Slater et al. (1984) [302], Flaggl et al. (1988) [82], and Wells et al. (1990) [339] noticed retinopathy with CWSs and hemorrhages in patients with pancreatic retinopathy with retinal infarctions. Semlacher & Chan-Yan (1993) [293] described the angiographical findings of retinal artery obstruction, and evidence of vessel leakage in areas corresponding to the CWSs in a 34-year-old man with retinopathy due to pancreatitis. Jacob et al. (1981) [132] found circulating granulocyte-aggregating activity in several patients with acute pancreatitis, assuming that complement-induced leukoembolization may cause damage to vital tissues. In patients with acute pancreatitis, the retinal changes may have resulted from posterior retinal arterial occlusion with clumped granulocytes. The aggregation of these granulocytes could be evoked by activated complement. Kincaid et al. (1982) [143] observed extensive ischemic infarcts at the posterior poles of both eyes in a 32-year-old woman, resembling Purtscher's retinopathy. Histological examination revealed arteriolar occlusions in both choroid and retina, and inner infarctions with retinal edema.

Shapiro & Jacob (1982) [294] described large CWSs with some hemorrhages in the posterior-pole region, particularly around the disc and extending to the macular area, due to acute pancreatitis in a 36-year-old man. As in acute pancreatitis, the plasma complement cascade is frequently activated. This cascade can cause leukocyte aggregation with resultant leukoembolization. The authors collected the plasma from 12 alcoholic patients with acute pancreatitis. Eight demonstrated marked granulocyte aggregation activity, which proved under further analysis to reflect C5a, the activated complement component. C5a can be produced by activation of the proteolytic enzyme trypsin. In acute pancreatitis trypsin often leaks from the inflamed pancreas into the bloodstream. The authors postulated that circulating C5a is generated in pancreatitis via this leakage.

Mayer (1985) [196] noticed that retinopathy rarely occurs in patients with pancreatitis. The author argued that blood vessel occlusions do not adequately explain the severe morphological changes and malfunctions of the retina. Sanders et al. (1992) [265] reported Purtscher's retinopathy in a 30-year-old woman complaining of impaired vision. The retinopathy preceded an acute pancreatitis, which occurred two weeks after the visual deterioration.

Hollo & Bobek (1993) [126] emphasized that CWSs may occur without vascular obstruction in severe acute

pancreatitis. Disruptions in axoplasmic transport, leading to CWS may develop without embolization or mechanical vascular occlusion. Retinal vessels around the CWSs were intact in a 36-year-old patient during recurrent acute necrotizing pancreatitis.

13.16 Malignant diseases

CWSs in patients with pancreatic carcinoma

Tabandeh et al. (1999) [318] described hemorrhages and large peripapillary yellow-white patches within the superficial retina similar to CWSs in a 63-year-old woman suffering from mucinous pancreatic adenocarcinoma. The authors maintain that the changes may have been associated with subclinical pancreatitis or, alternatively, as a pre-symptom of pancreatitis. Due to tumor growth, damage to the pancreas, involving release of activated protease enzymes, could have triggered a cycle of complement activation and microvascular occlusion.

Schmidt et al. (2001) [277] observed CWSs in both eyes of two patients suffering from metastasizing pancreas cancer. Visual acuity and field were normal in the 62-year-old woman, and reduced in one eye of the 47-year-old man. It seems that a mechanism similar to that in pancreatitis occurs in patients with pancreatic carcinoma.

Carcinoma of the liver

Streiff & Bischler (1943) [315] reported on distinct dilated retinal veins with CWSs in two patients, 60 and 79 years old with jaundice due to liver cancer.

CWS in bronchogenic carcinoma

Kiewe & Hart (1951) [139] described a small, whitish, very slightly raised lesion on the nasal side of the disc in the fundus of the left eye of a 47-year-old male with bronchogenic carcinoma. A nest of cytooid bodies situated in the retinal nerve-fiber layer were found in a series of sections.

CWS in multiple myeloma

Shami & Uy (1996) [296] described one CWS in each eye of a 67-year-old woman. The patient complained of a blurry circle in her right eye lasting three days. The CWS triggered intensive diagnostic investigation to identify a systemic disease. Protein electrophoresis and bone marrow aspirate lead to the diagnosis of multiple myeloma. The authors reiterated that the presence of a single CWS in a normal fundus should alert clinicians to the possibility of a serious systemic disease, which is why thorough systemic evaluation is necessary.

Leukemia

In acute forms of leukemia, CWSs are common. Occlusions of retinal vessels can occur, producing retinal infarctions (Spencer 1996) [307]. Lang et al. (1998) [173] reported that hematological disorders can manifest in all the structures of the eye. The most common manifestations are conjunctival pallor and hemorrhages, intraretinal hemorrhages and CWSs. Schmidt & Möbius (1975) [270] described white-centered hemorrhages in leukemia. Some hemorrhages contained a white component owing to the presence of leukemic

cells. These white centers are not CWSs. Brown et al. (1985) [39] reported that CWSs with leukemia may occur secondary to anemia, or - which is more likely - from obstruction of the vessels by leukemic cells.

Kincaid & Green (1983) [144] found that CWSs often coincide with leukemia. They reported that CWSs are due to ischemia from anemia, hyperviscosity, or leukemic infiltration. Cytooid bodies were found histologically in nine patients. In a prospective study, El-Asrar et al. (1996) [75] reported that the presence of CWSs in patients with leukemic retinopathy indicating a poor prognosis in acute leukemia. Their study enrolled 54 newly-diagnosed patients with acute leukemia. Those patients with CWSs were about eight times more likely to succumb to the disease than those without CWSs. Guyer et al. (1989) [107] examined 117 patients with acute leukemia. Intraretinal hemorrhages, white-centered hemorrhages and CWSs were all found more frequently in adults than in children. The presence of CWSs did not correlate with hematologic parameters. Reddy & Menon (1998) [255] examined 82 children with leukemia, detecting ocular changes in 14 patients (17%). Ten children had lymphoblastic, and four myeloid leukemia. The ocular lesions observed were proptosis, retinal hemorrhages, white-centered hemorrhages, CWSs, macular hemorrhages, vitreous hemorrhages, and papilledema.

CWSs in Hodgkin's disease

Brihaye-van Geertruyden (1956) [37] observed CWSs in a 31-year-old anemic patient with Hodgkin's disease. The CWSs resolved after radiation therapy, although they relapsed about two months later. The histologic postmortem examination revealed cytooid bodies.

Systemic non-Hodgkin's lymphoma

Cho & Yoon (2003) [52] reported rapidly-developing CWSs in one eye as the first manifestation of systemic non-Hodgkin's lymphoma in a 63-year-old man. Because of the marked increase in CWSs after four weeks, a liver biopsy was carried out. The cause of the progressive systemic disease was a large diffuse B-cell lymphoma. The CWSs had completely disappeared after chemotherapy and prednisone.

Drug induced systemic vasculitis in carcinoma

Banach & Williams (2000) [20] reported necrotizing vasculitis due to treatment with Gemcitabine in a 59-year-old man with a 10-year history of diabetes. The patient had begun treatment with gemcitabine hydrochloride for lung cancer. The retina revealed CWSs and intraretinal hemorrhages in the posterior pole of each eye. The authors concluded that gemcitabine may induce systemic vasculitis with ESR and ANA elevation, which may lead to Purtscher-like retinopathy.

13.17 Drug-induced side effects

Retinopathy due to interferon treatment

Interferon associated retinopathy with CWSs has been reported by Harada et al. (1995) [111], Hayasaka et al. (1998) [113], Hoerauf et al. (2000) [124], Neubauer & Hoops (2000) [222], Schulman et al. (2003) [290], Stoffelns (2006) [310], and Mantel et al. (2007) [190].

Interferon has often been utilized for treating hepatitis C. The occurrence of retinal changes depends on the interferon dosage. Harada et al. (1995) [111] observed retinopathy with CWSs and hemorrhages in four patients, five to 30 days after the beginning of interferon therapy. Hayasaka et al. (1998) [113] found non-perfused areas with CWSs by fluorescein angiography. CWSs and retinal hemorrhages developed two weeks to three months after the start of interferon therapy. They discovered that the initial dose of interferon is essential for retinopathy to develop. A pre-existing retinopathy should be excluded before the starting interferon therapy.

Hoerauf et al. (2000) [124] described CWS formation and small retinal hemorrhages in a 40-year-old man treated with IFN alfa-2b for metastatic renal-cell carcinoma. Late phase-fluorescein angiography revealed venous dilatation and retinal vessel leakage in both eyes. Indocyanine-green-angiography (ICGA) showed a well-demarcated area of confluent and persistent choroidal filling defects. Visual acuity had decreased to 20/50. Neubauer & Hoops (2000) [222] observed bilateral microangiopathy with CWSs and unilateral visual loss in a 58-year-old woman due to interferon treatment. The patient suffered from a malignant cutaneous melanoma. After discontinuation of treatment, the retinal changes were reversible. Schulman et al. (2003) [290] observed retinopathy in 29 of 42 patients (69%) with hepatitis C being treated with interferon alpha 2b and ribavirin. Single-to-multiple CWSs and retinal hemorrhage occurred in 27 patients; they were transient in all patients. CWSs appeared as early as two weeks after initiation of interferon therapy, or up to several months later. Kirchhoff et al. (2004) [146] observed bilateral AION but no CWSs in a 51-year-old man who had been treated with interferon and ribavirin for hepatitis C. Stoffelns (2006) [310] reported on 12 patients treated with interferon-alpha for hepatitis C, metastatic renal cell carcinoma, leukemia, or malignant melanoma of the skin. Macular edema, retinal arteriolar occlusion or AION were seen in some eyes. After an interruption (10x) or dose reduction (2x) of interferon therapy, the ischemic changes disappeared rapidly in all eyes.

Mantel et al. (2007) [190] reported on a 63-year-old man with hepatitis C presenting interferon-induced retinopathy with some CWSs, partially white centered, flame-shaped hemorrhages, and microaneurysms on both fundi.

13.18 Purtscher's retinopathy is more than an ischemic state

Definition of Purtscher's retinopathy

Behrens-Baumann & Scheurer (1991) [22] highlighted the main characteristics in Purtscher's retinopathy in eleven patients. These are:

- 1) yellowish-white "Purtscher-Flecken" which have a polygonal margin and lie in the inner nuclear layer between the arterioles,
- 2) typical white CWSs located in the nerve-fiber layer covering the vessels and hemorrhages.

They described 10 patient with retinopathy caused by trauma to the thorax, skull and one by pancreatitis.

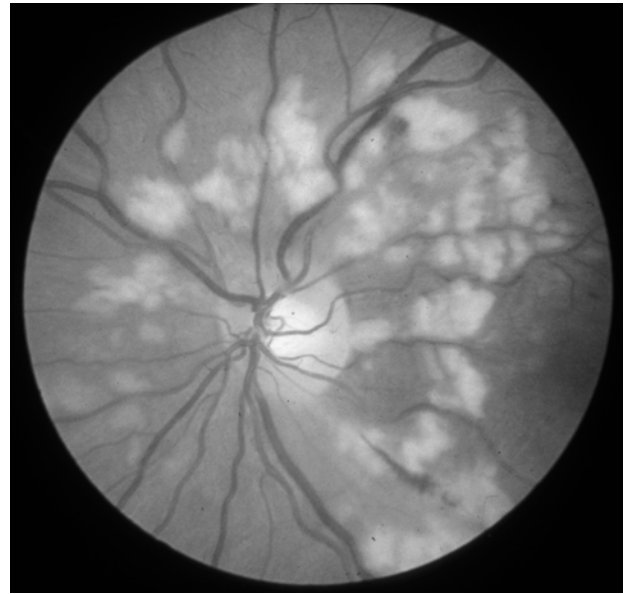


Fig. 15. Purtscher's retinopathy with polygonal margins of white spots in a 30-yearold man after a traffic accident.

White retinal areas between retinal vessels with a polygonal outline were called "Purtscher-Flecken".

Behrens-Baumann et al. (1992) [23] observed that "Purtscher-Flecken" never cover vessels. They are typically polygonal in shape, and never adjoin the arterioles.

Gibson et al. (2000) [93] described "Purtscher-Flecken" as areas of retinal whitening due to occlusion of the deeper retinal capillary bed. Schmidt & Otto (2004) [282] compiled the data of 10 patients with Purtscher's retinopathy who were examined in the Eye Hospital Freiburg, the data of 55 patients with Purtscher's retinopathy, and 20 patients with traumatic retinal hemorrhages published in the literature. In all 65 Purtscher's retinopathy patients, the fundi revealed typical "Purtscher-Flecken" in 48 eyes and CWSs in 33 eyes. Retinal hemorrhages were detected in 61 eyes (82.4 %).

Pathophysiology of Purtscher's retinopathy

Purtscher (1910) [250] described bright white retinal spots and hemorrhages in a 49-year-old man after a severe skull trauma after a fall from four meters. Purtscher observed 29 white retinal spots of different size and configuration which concealed several retinal veins and were located in the innermost retinal layer. They reminded him of scattered snow flakes with blurred margins. Purtscher used the term "angiopathia traumatica retinae" for these retinal posttraumatic changes. He argued that cerebrospinal fluid had been forced into retinal lymphatic perivascular space. Purtscher (1912) [251] again described bright white retinal spots adjacent to the optic disc and macular region, suggesting that the white retinal lesions may be lymphatic extravasations from retinal vascular injury caused by a sudden increase in intracranial pressure. Marr & Marr (1962) [191] described superficial whitish areas resembling CWSs which were scattered around the posterior pole in a 48-year-old man after severe

chest compression. The white areas varied in size from one-sixth to one-third disc diameter. They gradually became less intense, and were barely visible two months after the accident.

The pathogenesis of Purtscher's retinopathy was explained by traumatic asphyxia due to a hydrostatic pressure syndrome with retinal vascular damage from reflux venous shock waves caused by the sudden rise in intrathoracic pressure accompanying chest compression.

Baarsma & Van Balen (1977) [18] observed angiographically non-perfusion areas with closure of the preterminal arterioles and venules in an 8-year-old boy after an accident involving compression of the chest. The dilated veins and retinal hemorrhages indicated a sudden rise in intraluminal pressure, while capillary closure and arterial changes suggested some form of micro-embolization.

Burton (1980) [43] published unusual findings of unilateral Purtscher's retinopathy in four patients, explaining the pathogenesis of Purtscher's retinopathy via air embolization, caused perhaps by air from the lungs in thoracic trauma. Angiographic and clinical features suggested a vaso-occlusive process involving the choroid and optic nerve as well.

Orzalesi & Coghe (1980) [229] reported on two patients with unilateral traumatic Purtscher's retinopathy, explaining that the retinal features were caused by a traumatic increase in cephalic venous pressure, which may have led to subconjunctival hemorrhage and retinal venous stasis, followed by hemorrhages and ischemic changes, similar to capillary non-perfusion and CWSs. The CWSs were found in association with capillary non-perfusion as a result of obstruction of orthograde and retrograde axonal flow in ganglion cell axons. A nerve-fiber bundle defect was found after recovery of CWSs by ophthalmoscopy and perimetry. Gass (1987) [91] suggested that arteriolar leakage in Purtscher's retinopathy associated with traumatic acute endothelial damage may predispose the retinal vascular tree to intravascular coagulopathy or granulocyte aggregation, leading to multiple arteriolar obstruction. Archer (1988) [6] reported on three patients involved in traffic accidents who had sustained seat-belt-related injuries. He maintained that the acute arteriolar changes may be due to a momentary interruption in blood flow to the eye which might be induced by acute neck flexion or sudden head movements, causing direct injury to the carotid/ophthalmic artery complex with subsequent retinal-vessel spasm. He also argued that the traumatic angiopathy was triggered by acute chest compression, in particular against a closed glottis, in turn causing high venous wave of pressure to be transferred to the eye vessels. Behrens-Baumann & Scheurer (1991) [22] believed that the pathogenesis of Purtscher's retinopathy lie in microembolization caused by intravascular coagulation and/or the aggregation of leukocytes or thrombocytes. Behrens-Baumann et al. (1992) [23] reported that small vessel microembolization could be caused by activation of the complement system with C5a-induced leukocyte aggregates formation. The pathogenesis of Purtscher's retinopathy should not attributed to the mechanical hypothesis, since

retinopathy has been observed in patients without trauma in acute pancreatitis. Intravascular coagulation can occur following trauma or acute pancreatitis. Microparticles may be caused by aggregated leukocyte platelets or fibrin clots. Experimental animal examinations with fibrin clots of different size that were injected into the ophthalmic artery in animals caused superficial and deep retinal infarctions. The ophthalmoscopic characteristics of experimental Purtscher's retinopathy after embolization were CWSs, "Purtscher-Flecken" and retinal hemorrhages.

Blodi (1990) [32] described severe bilateral visual loss due to multiple retinal arteriolar occlusions in four young women within 24 hours after childbirth. Ophthalmoscopy revealed retinal changes simulating Purtscher's retinopathy. The white retinal patches resolved within eight weeks, and visual acuity improved in three patients. To explain this disorder, the author hypothesized that arteriolar obstruction occurred by complement-induced leucoemboli formed during parturition. Fundi with no signs of systemic fat embolism accompanying head trauma, chest compression, or pancreatitis show larger, more confluent ischemic retinal patches which are confined mainly to the peripapillary retina.

Gibson et al. (2000) [93] observed multiple hemorrhages, CWSs, and "Purtscher-Flecken" close to the optic disc in a 38-year-old woman after a traffic accident.

Schmidt & Otto (2004) [282] described Purtscher's retinopathy accompanied by a distinct loss of vision as a result of severe trauma to the chest or skull. In spite of severe initial retinal findings, the visual prognosis is usually not so dire. Patients with traumatic retinal hemorrhages without CWSs and without "Purtscher-Flecken" were compared with patients presenting the signs of typical Purtscher's retinopathy. Visual-acuity prognosis was better in patients with traumatic retinal hemorrhages than in those with Purtscher's retinopathy.

Findings in Purtscher's retinopathy

Monocular Purtscher's retinopathy was observed in patients described by Vogt (1923) [333], Pratt & De Venecia (1970) [247], Fischbein & Safir (1971) [81], Ravin & Meyer (1973) [254], Burton (1980) [43], Orzalesi & Coghe (1980) [229], Shiono & Kimura (1980) [299], Teichman & Gronemeyer (1981) [320], Fellingner & Kunz (1986) [78], Stassen et al. (1989) [309], and Schmidt & Otto (2004) [282].

Vogt & Knüsel (1921) [332] found bilateral, multiple, roundish, white, partly confluent retinal patches temporal to the papilla and hemorrhages in the eyes of a 24-year-old man after a fall on the back of his head. Vogt (1923) [333] observed white, roundish patches in the superficial retinal layer, partly covering mostly the retinal veins in a 28-year-old man after a trauma with fracture of the base of the skull.

Schieck (1930) [269] described bright white spots adjacent to retinal veins largely near the papilla showing blurred margins; some covered retinal vessels. Stokes (1932) [312] described contracted retinal arteries, and veins full and congested. In addition, there were many discrete, elevated, whitish patches, some confluent and resembling CWSs. Massive hemor-

rhages were observed in a 56-year-old man after a car accident. Löwenstein (1936) [181] reported silver-white or cloudy-gray spots in the superficial retinal layer of a 31-year-old man who had suffered from a thoracic trauma.

Bedell (1939) [21] noticed that the entire retinal posterior pole consisted of an immense, milky-white swelling obscuring the disc and covering the retinal vessels, "resembling a collection of large cumulous clouds in the bright blue sky on a hot summer afternoon" in a 21-year-old man with a head injury after an automobile accident. There were many superficial hemorrhages.

Pratt & De Venecia (1970) [247] observed CWSs, hemorrhages, optic atrophy, and retinal venous engorgement in a 33-year-old man after a skull injury.

Fischbein & Safir (1971) [81] noted monocular Purtscher's retinopathy in a 24-year-old man after an automobile accident. The fundus revealed hemorrhages, exudates, dilated and tortuous veins, and macular edema. The superotemporal vein was partially obstructed.

Madsen (1972) [185] described Purtscher's retinopathy in nine patients. The fundus changes consisted in venous stasis and exudation in all cases, and hemorrhages in most. Ravin & Meyer (1973) [254] reported on a unilateral papilledema with CWSs and hemorrhages in a 13-year-old boy after severe chest compression. Fellingner & Kunz (1986) [78] observed unilateral Purtscher's retinopathy after thoracic trauma in a 19-year-old man. The retinal veins were conspicuously dilated and tortuous; along the congested veins, white confluent intra- and preretinal exudates were observed. Archer (1988) [6] reported on retinal angiopathy characterized by retinal hemorrhage, edema, and focal ischemia in three patients. A 46-year-old female showed thoracic bruising from the seat belt. Within one hour of the accident, she complained of poor vision. The retina in one eye revealed multiple peripapillary CWSs and scattered intraretinal hemorrhages at the posterior pole, and a subhyaloid hemorrhage. Angiography revealed arterial stasis. Stassen et al. (1989) [309] found blurring of the nasal margin of the optic disc with peripapillary CWS formation in a 45-year-old man after a traffic accident. Shibata (1994) [298] observed Purtscher's retinopathy with CWSs and hemorrhages sited in the posterior pole in a 20-year-old man, who suffered multiple crush injuries. His visual acuity was reduced to light perception.

Optical coherence tomography (OCT) in Purtscher's retinopathy
Meyer et al. (2006) [211] examined CWSs in Purtscher's retinopathy in a 15-year-old boy who noticed sudden, painless visual loss after a frontal head injury due to a traffic accident. Optical coherence tomography (OCT III) of the peripapillary retina revealed a localized hyporeflexive area corresponding to CWSs in the retinal nerve-fiber layer. The CWSs significantly decreased in number and size four weeks later. The OCT examination no longer depicted a hyporeflexive area.

Fluorescein angiography in Purtscher's retinopathy

Burton (1980) [43] reported the symptoms of four pa-

tients with unilateral Purtscher's retinopathy such as impaired arteriolar flow, capillary non-perfusion, venous staining, retinal edema, and optic disc edema in angiographic investigation.

Shiono & Kimura (1980) [299] noticed fluorescein angiographic changes in the left eye of a 44-year-old male with areas of capillary non-perfusion corresponding to the CWSs regions. Some capillaries were dilated. There was leakage of dye into the retina from the capillaries in the CWS area. The authors also observed a week after the accident several hemorrhages around the CWSs in the affected eye not visible at the first examination. Teichman & Gronemeyer (1981) [320] described angiographic findings such as hypofluorescent areas in the arterial phase corresponding to retinal edema in a 25-year-old man after a car accident. The late phase demonstrated staining and occlusion of venules and arterioles. Hirsch & Mertz (1981) [121] found fluorescein-angiographic retinal changes in a 19-year-old man after a car accident; observing venous congestion, multiple occlusions of tiny arterioles, and destruction of the capillary network in the posterior pole. Gass (1987) [91] described filling defects and obscuration of the capillary bed in the white retinal lesion area, stating that in mild retinopathy, dye leaking from the retinal arterioles, capillaries, and venules in the area around the white lesions can occur. However, arteriolar obstruction and leakage in the region around the white patches were found in more severe retinopathy. Tso & Jampol (1990) [325] noticed areas of nonperfusion around the CWSs. Retinal capillary dilatation, accompanied by microaneurysms, capillary telangiectasia, and capillary non-perfusion surrounded the CWSs. Collaterals with beaded vascular channels and damage to the vessel wall, with reduced blood flow occurred, resulting in ischemia.

Purtscher's-like retinopathy in chronic renal failure

Stoumbos et al. (1992) [314] described blurred disc margins with multiple ischemic retinal whitening and edema extending circumferentially from the optic nerve. By fluorescein angiography, widespread retinal arteriolar occlusions, capillary nonperfusion, and late staining of retinal vessels were observed in a 23-year-old woman who suffered sudden, painless visual loss in her right eye due to a history of glomerulonephritis with chronic renal failure.

13.19 Retrobulbar anesthesia

Retinal changes as in Purtscher's retinopathy were observed after retrobulbar injections for anesthesia of the eye by Lemagne et al. (1990) [175], Blodi & Williams (1997) [33], and Lim & Ang (2001) [179]. Fluorescein angiography was carried out in all patients. Lemagne et al. (1990) [175] described on hypoperfusion and delayed perfusion of some peripapillary arterioles. Blodi & Williams (1997) [33] found areas of capillary nonperfusion corresponding to retinal whitening. The visual field depicted a dense cecocentral scotoma. Lim & Ang (2001) [179] demonstrated an area of retinal hypoperfusion superotemporal to the optic disc, as well as peripheral arteriolar occlusions.

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