De novo lesions in presumed ocular histoplasmosis-like syndrome

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The presumed ocular histoplasmosis syndrome (POHS) has been amply described (Krill, Chishti, Klein, Newell, and Potts, 1969; Schlaegel, Weber, Halverston, and Keeney, 1967; Makley, Long, Usre, and Stephens, 1965; Maumenee, 1965; Gass, 1967; Woods and Wahlen, 1960; Krause and Hopkins, 1951; Van Metre and Maumenee, 1964; Schlaegel, 1975; Gass and Wilkenson, 1972) and in its complete form is characterized by five features:

1. A disciform macular lesion.

This report has been supported in part by Public Health Service grant number EY 00039 from the National Eye Institute, National Institute of Health, Washington DC

Presented before the Association for Research in Vision and Ophthalmology, Sarasota, Florida, April 1976

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2. Multiple small punched-out choroidal atrophic lesions in the fundus periphery.
3. Peripapillary scarring.
4. Absence of inflammatory cells in the vitreous.
5. A positive histoplasmin skin test.

Many cases included in reports concerning this syndrome lack one or more of these features (Krill and others, 1969; Gass, 1967; Woods and Wahlen, 1960; Schlaegel, 1975; Braunstein, Rosen, and Bird, 1974).

Patients with a full-blown haemorrhagic disciform macular lesion in one eye frequently have one or more inconspicuous circumscribed white spots in the posterior pole of the fellow eye. Most observers believe that when a haemorrhagic disciform lesion arises in the second eye it does so from such a previously asymptomatic paramacular lesion (Krill and others, 1969; Schlaegel, 1975; Gass and Wilkenson, 1972; Smith, Knox, and

FIG. 1a. 2 April 1970. Disciform macular lesion right eye. Centre subretinal greyish pink fibrovascular mounds surrounded by subretinal haemorrhage. Compare subtle choroidal lesions with fluorescein angiography (Fig. 1b) and follow-up photographs (Figs 3a, b)

FIG. 1b, c Fluorescein angiogram right eye on same day confirming presence of a subretinal neovascular membrane and showing retinal pigment epithelial window defects at site of arrows in Fig. 1 as well as two additional pigment epithelial defects temporal to fovea

Jenson, 1973; Sawelson, Goldberg, Annesley, and Tomer, 1976). Fluorescein angiography is sometimes necessary to detect these lesions, which may be unapparent ophthalmoscopically (Krill and others, 1969; Gass and Wilkenson, 1972; Hyzarinen, Lerer, and Knox, 1971). Gass and Wilkenson (1972) have documented the development of a new peripheral lesion. Krill (1971) and Schlaegel (1972, 1974) have occasionally observed that typical macular disciform lesions develop in second eyes

which had previously appeared normal ophthalmoscopically, but they have not reported such cases in detail. Recently, Ryan (1976) has reported a carefully documented case of de novo subretinal neovascularization in POHS.

In this report two cases are considered of multifocal choroiditis similar to or identical with POHS in which new lesions developed, at some time after an initial disciform process, in the retina which appeared normal ophthalmoscopically and

FIG. 2a 2 April 1973. Black and white print from colour photographs of normal left eye

FIG. 2b 2 April 1973. Normal fluorescein angiograms of left eye

with fluorescein angiography. These 'de novo' lesions are documented as occurring not only in the initially involved eye, but also in the originally uninvolved eye.

Patients and methods

CASE REPORT I

A 39-year-old White man who had been under heavy business pressure noted blurred vision shortly after

accidentally striking his right brow against the edge of a cabinet. He was seen shortly after this event by his local ophthalmologist who diagnosed POHS, started him on oral prednisone, and referred him for consultation in three weeks' time.

On our initial examination on 2 April 1973, the visual acuity with correction was 20/50 right eye and 20/20 left. The refractive error was $-7.25 + 4.00$ axis 100 in the right eye and $-7.50 + 3.50$ axis 78 in the left. Slit-lamp biomicroscopy of the anterior segment and vitreous was normal. Both eyes demonstrated a narrow zone of de-

FIG. 3a 8 August 1975.
Hypertrophic macular scar right eye. Previous choroidal lesions are more distinct and new lesions are noted (arrow inferotemporal to disc indicates one such lesion). (Arrow inferonasal to disc points to distinct peripapillary activity)

FIG. 3b 8 August 1975.
Fluorescein angiogram right eye confirms presence of previous subtle lesions and presence of new choroidal lesions

pigmentation surrounding the disc. This was thought to represent a congenital myopic conus, although no other signs of myopic degeneration were present. Neither eye had peripheral atrophic lesions. Abutting the right fovea was a typical 'signet ring' lesion characterized by a roundish greyish to pinkish centre surrounded by dark 'pigment', which in turn was surrounded by a collarette of subretinal haemorrhage (Fig. 1a). Three

small (less than 250 μm in diameter) circumscribed white spots were present, two in the perimacular area (Fig. 1 arrows) and one nasal to the disc. Fluorescein angiography confirmed the presence of subretinal neovascular membrane within the signet ring and a focal detachment of the overlying sensory retina (Figs 1b, c). Hyperfluorescence typical of retinal pigment epithelial defect was noted at these three sites as well as at two

FIG. 4a 8 August 1975. Left eye has a linear subretinal greyish membrane incompletely surrounded by subretinal and intraretinal haemorrhages. Other subtle lesions are present. (Example arrow)

additional sites temporal to the macula (Figs 1a, b, c). Photography (Fig. 2a) and stereoscopic fluorescein angiography (Fig. 2b) performed on the left eye at that time showed a normal posterior pole.

Prednisone was gradually reduced and then discontinued, and the patient was followed-up by his local ophthalmologist. The patient was referred again on 8 August 1975. One week previously he had noted distorted vision and decreased visual acuity in his previously uninvolved left eye. Three days after the onset of symptoms, the referring ophthalmologist had again started the patient on prednisone. The visual acuity on 8 August was 8/200 in the right eye and 20/25 in the left. In the right eye there was a hypertrophic macular scar at the site of the original disciform lesion (Fig. 3a). There was depigmentation of the retinal pigment epithelium adjacent to this area. The three previously noted choroidal lesions were distinctly more prominent, and at least three additional choroidal lesions had appeared (Figs 3a, b). There was a definite peripapillary choroidal lesion inferonasally (Fig. 3a arrow). In the left eye there was a greyish subretinal lesion incompletely surrounded by subretinal and intraretinal haemorrhage (Fig. 4a). Subtle choroidal lesions were present (Fig. 4a arrow). Fluorescein angiography confirmed the presence of a subretinal neovascular membrane (Figs 4b, c). The lesion marked with an arrow in Fig. 4c is hypofluorescent in the early choroidal phase and normal fluorescent in the later phase. The patient was begun on systemic oral prednisone which was gradually reduced during the next three months. On 8 September 1975 the patient's visual acuity was 20/200 right eye and 20/60 left. The previously noted incomplete pigment ring and choroidal lesions were more predominant. The subretinal neovascular membrane network had partly coalesced. The choroidal

lesions marked with an arrow in Fig. 4a fluoresced at this time (Fig. 5) as well as new areas of fluorescence (arrow). Additional lesions were present below the posterior arcade.

CASE REPORT 2

A 36-year-old White woman was seen by us on 12 December 1972. She stated that seven years previously she had noticed decreased vision in her left eye. She was initially seen at the University of Iowa Hospital where a diagnosis of chorioretinitis was made and was treated with systemic and topical corticosteroids with some improvement. A histoplasmin skin test was negative. Her symptoms recurred in the autumn of 1972, and she was seen at the Mayo Clinic where a histoplasmin test was positive. The diagnosis of recurrent chorioretinitis presumed to be due to histoplasmosis was made. The patient was given retrobulbar corticosteroids.

On our initial examination on 12 December the corrected visual acuity was 20/10 right eye and 20/60 left. Slit-lamp biomicroscopy of the anterior segment and vitreous was normal. At that time no peripheral atrophic scars were noted in either eye. Peripapillary changes were present in both eyes. The right macular region appeared normal (Fig. 6). In the left eye (Fig. 7) there was a chorioretinal scar just temporal to the fovea. A second subretinal scar surrounded by a zone of subretinal haemorrhage was noted inferotemporally. Overlying both scars was a serous detachment of the sensory retina. ('Atrophic' choroid spots (Fig. 7 arrow) are present within the posterior pole). The patient failed to return at that time for fluorescein angiographic studies.

On 27 June 1973 she returned because vision in her left eye had decreased. The visual acuity was 20/20 left

FIG. 4b, c Case 1, 8 August 1975.

Fluorescein angiogram left eye confirms presence of a subretinal neovascular membrane. Early phase angiography suggests several foci of subretinal neovascularization. The choroidal lesion in Fig. 4a is hyperfluorescent early and (4b) normal fluorescent in late stages

eye and 20/200 right. No change in appearance of the right fundus was noted and stereo fluorescein angiography was normal (Fig. 8). In the left eye the subretinal haemorrhage had reabsorbed, and the subretinal fibrous tissue was now surrounded by an area of depigmentation. Fluorescein angiography (Figs 9a, b) showed a typical subretinal neovascular membrane with a prominent choroidal feeder and two cartwheel neovascular nets. There was minimal leakage from the sub-

retinal neovascular membrane and subretinal space. Neither corticosteroids nor photocoagulation was thought to be indicated at that time.

The patient returned on 8 March 1975 with a three-day history of a central scotoma in the visual field of her right eye. The visual acuity was 20/15 right eye and 10/200 left. Four white spots (Fig. 10a) were noted near the right fovea. On fluorescein angiography window-type pigment epithelial defects were noted in three of

FIG. 5 Case 1, 8 September 1975. Fluorescein angiography left eye showed tendency for lesion to coalesce. Previous choroidal lesion from Fig. 4a is now fluorescent as well as additional points of fluorescence (arrow Fig. 5)

FIG. 6 Case 2, 12 December 1973. Black and white print from colour photograph showed a normal-appearing macula (right eye)

the four lesions, but the lesion immediately temporal to the fovea (Fig. 10a arrow) did not fluoresce (Fig. 10b). Metamorphopsia was noted on Amsler grid. No central defect could be demonstrated on the tangent screen. On 20 March the visual acuity was 20/15 right eye and 20/40 left. The patient was started on prednisone 50 mg every other day, but since her symptoms persisted despite a stable visual acuity, this was increased to 100 mg every other day. During the next four weeks, she continued to have symptoms. No scotoma could be

demonstrated in the right eye with the o 2E test object on the Goldmann perimeter. In the left eye there was a dense pericentral scotoma to the 5 4E test object. Colour vision was normal using the Farnsworth D-15 panel.

No reason could be found for the patient's persistent symptoms. Over the ensuing five months the prednisone was gradually reduced to 50 mg every other day and then maintained at that level.

On 8 August all four choroidal lesions were more

FIG. 7 Case 2, 12 December 1973.
(Left eye) chorioretinal scar just temporal to fovea. A small scar is present inferotemporally, partially surrounded by zone of subretinal haemorrhage. Not shown on the photograph is an overlying serous detachment of the sensory retina. 'Atrophic' choroidal scars (arrows) are present within posterior pole

FIG. 8 Case 2, 27 June 1973.
Fluorescein angiography right eye shows no abnormalities except peripapillary scarring

pronounced. Fluorescein angiography at this time showed, in addition to the three window-type defects present on 8 March, slight fluorescence of the lesion temporal to the fovea (Figs 11a, b compare with Figs 10a, b).

On 10 September 1975 visual symptoms had markedly lessened. A peripheral fundus examination repeated at this time showed four peripheral punched-out atrophic lesions in the right eye and no peripheral

fundus abnormalities in the left. Fundoscopy examination on 12 November 1975 showed less prominence of the choroidal lesion temporal to the fovea in the right eye and no serous subretinal fluid in the left.

Discussion

The initial and later stereoscopic fluorescein angiography and fundus photograph findings are

FIG. 9a, b Case 2, 27 June 1973. Choroidal feeder left eye clearly visible to dumbbell shape frond of subretinal neovascular membrane. Minimal subretinal fluid is not evident. There was surrounding area of depigmentation

summarized in Table I. There are five points to consider in the cases (Table I).

PATIENT 1 initially had a subretinal neovascular membrane and a disciform process. He did not have 'peripheral' atrophic lesions, but rather circumscribed yellowish white spots within the posterior pole of the originally involved eye. He had peripapillary depigmentation thought to repre-

sent a congenital myopic conus. He did not have vitreous cells, and was not skin tested. This patient went on to develop subretinal neovascular membrane and a paramacular disciform process in his originally uninvolved eye that had been normal ophthalmoscopically and angiographically. He developed new choroidal white spots in the posterior pole in the originally involved as well as the un-

FIG. 10a Case 2, 18 March 1975.
Four small choroidal lesions now
visible (right eye)

FIG. 10b Case 2, 18 March 1975.
Late venous phase fluorescein
angiogram (right eye) shows retinal
pigment epithelial window-like
defects in two and perhaps three of
four choroidal lesions. Lesion
temporal to the fovea (see Fig. 10a
arrow) does not fluoresce at this
time, but does later (see Fig. 11b)

involved eye, and he developed at least one definite peripapillary scar and some roughening of a presumed myopic conus.

PATIENT 2 initially had a subretinal neovascular membrane and a disciform process. She did not have peripheral atrophic lesions, but did have

bilateral peripapillary scarring. She did not have inflammatory cells in the vitreous, and a histoplasmin skin test was negative. She went on to develop four choroidal white spots in the macular area of the originally uninvolved eye which had been normal ophthalmoscopically and angio-

FIG. 11a Case 2, 8 August 1975. Choroidal lesions (right eye) are more pronounced. Large round spot adjacent to fovea at 5 o'clock is a photographic artefact

FIG. 11b Case 2, 8 August 1975. Venous phase of fluorescein angiogram (right eye) shows, in addition to retinal pigment epithelial window-type defects of 8/75, slight fluorescence of the lesion temporal to the fovea (see Figs 10a, b)

graphically. She also developed peripheral atrophic lesions in the originally uninvolved eye, and her histoplasmin skin test became positive.

The age, race, sex, geography, emotional or physical stress, and bilaterality represented by these two cases of POHS are consistent with those factors described in large surveys as typical of

POHS (Krill and others, 1969; Schlaegel and others, 1967; Makley and others, 1965; Maumenee, 1965; Gass, 1967; Woods and Wahlen, 1960; Krause and Hopkins, 1951; Van Metre and Maumenee, 1964; Schlaegel, 1975; Gass and Wilkenson, 1972).

Both patients are middle-aged Caucasians living near the Mississippi River who relate a history of

Table I Summary of cases. Initial presentation and findings on follow-up examination

Symptom	Case 1		Case 2	
	Originally involved eye	Originally uninvolved eye	Originally involved eye	Originally uninvolved eye
Subretinal neovascular membrane				
Initial	Present	Not present	Present	Not present
Later	Present	Present	Present	Not present
Atrophic white spot				
Central 30°				
Initial	Present	Not present	Present	Not present
Later	Present	Present	Present	Present
Peripherally				
Initial	Not present	Not present	Not present	Not present
Later	Not present	Not present	Not present	Present
Peripapillary atrophy				
Initial	Questionable	Questionable	Questionable	Questionable
Later	Present	Questionable	Present	Questionable
Vitreous cell				
Initial	Not present	Not present	Not present	Not present
Later	Not present	Not present	Not present	Not present
Histoplasmin skin test				
Initial	Not done	Not done	Not present	Not present
Later	Not done	Not done	Present	Present

Table II 'Classic' POHS. Percentage of reported series conforming to classic POHS and variation in macular findings

Demography	
Age	4th decade
Race	Caucasian
History of emotional or physical stress	Present
Region	Mississippi Valley
Macula of second eye	
Macular involvement initially (all forms)	56 to 67 per cent
Asymptomatic atrophic spot initially	24 to 36 per cent
Activation of atrophic spot on funduscopy	20 to 24 per cent
Involvement on funduscopy initially normal	0 to 2 per cent
Peripheral spots	Multiple (greater than 5) posterior to equator or in peri-equatorial zone
New spots	Rarely
Peripapillary lesions in one or both eyes	70 to 85 per cent
Histoplasmin skin test	
America	90 to 100 per cent
England	0 per cent

emotional and/or physical stress. Both have bilateral involvement with severe loss of visual acuity associated with haemorrhage in at least one eye.

There are several exceptions and variations noted in the reporting of the POHS (Table II). First, some reports, especially earlier ones, have included cases with some vitreous cells. Secondly, 10 per cent of American cases and virtually all British ones have a negative skin test (Braunstein and others, 1974). Thirdly, at least 25 per cent of patients do not have peripapillary scarring (Schlaegel and others, 1967; Schlaegel, 1974). Fourthly, epidemiological surveys attempting to characterize peripheral atrophic choroidal scars (Krause and Hopkins, 1951) in POHS have greatly clarified the appearance of these spots. Yet there are no rigid criteria for (a) 'peripheral' (? extra macular, posterior pole, equator, etc.), (b) number of lesions and appearance of these spots. Not surprisingly inclusive criteria in various reports range from 'every patient had more than one lesion' to 'typical findings' of POHS.

The reader at this point has decided whether he or she accepts both, neither, or one of the cases as 'presumed ocular histoplasmosis syndrome', an unrecognized form of retinal pigment epithelio-

pathy, or multifocal choroiditis of unknown aetiology. The most significant observations in these two cases are the occurrence of new choroidal lesions in the previously uninvolved eye as documented ophthalmoscopically and by fluorescein angiography, the development of new choroidal lesions within the originally involved eye, documentation and early evolution of the initial 'basic lesion' (Figs 4, 5, 10, and 11 arrow), and the need for angiography for visualizing underlying choroidal lesions.

Patients with POHS-like lesions in one eye and a normal posterior fundus in the other should not be given an unequivocally good prognosis for the second eye.

Summary

Two patients with multifocal choroiditis similar or identical to POHS are presented. Colour photographs and fluorescein angiography document the

occurrence of de novo lesions in the originally involved eye. The cases also demonstrate the development of new choroidal lesions within the originally involved eye, the early evolution of the 'basic choroidal lesion', and the need for fluorescein angiography for visualizing the underlying choroidal lesion.

Addendum

Since submitting this paper Wilkinson (1976) has documented the appearance of de novo lesions in presumed ocular histoplasmosis. Cleasby (1976) has reported on 20 patients with neovascular membranes resembling those seen in POHS, but without any associated characteristic ophthalmoscopic findings considered necessary to make a diagnosis of POHS.

We thank Dr Alan A. Ehrhardt for referring one of the patients and Dr M. D. Davis for his guidance in preparing this manuscript.

References

- BRAUNSTEIN, R. A., ROSEN, O. A., and BIRD, A. C. (1974) *Brit. J. Ophthalm.*, **58**, 893
 CLEASBY, G. W. (1976) *Amer. J. Ophthalm.*, **81**, 590
 GASS, J. D. M. (1967) *Ibid.*, **63**, 661
 ———, and WILKINSON, C. P. (1972) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **76**, 672
 HYZARINEN, L., LERER, R. J., and KNOX, D. L. (1971) *Amer. J. Ophthalm.*, **71**, 449
 KRAUSE, A. C., and HOPKINS, W. G. (1951) *Ibid.*, **34**, 564
 KRILL, A. E. (1971) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **75**, 664
 ———, CHISHTI, M. I., KLEIN, B. A., NEWELL, F. W., and POTTS, A. M. (1969) *Ibid.*, **73**, 222
 MAKLEY, T. A., LONG, J. W., USRE, T., and STEPHENS, J. D. (1965) *Ibid.*, **69**, 443
 MAUMENEE, A. E. (1965) *Ibid.*, **69**, 605
 RYAN, S. J. (1976) *Arch. Ophthalm.*, **94**, 321
 SAWELSON, H., GOLDBERG, R. E., ANNESLEY, W. H. JR., and TOMER, T. L. (1976) *Ibid.*, **94**, 221
 SCHLAEGEL, T. F. JR. (1972) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **76**, 693
 ——— (1974) *Ann. Ophthalm.*, **6**, 237
 ——— (1975) 'Ocular Histoplasmosis'. Little Brown, Boston
 ———, WEBER, J. C., HALVERSTON, E., and KEENEY, D. (1967) *Amer. J. Ophthalm.*, **63**, 919
 SMITH, R. E., KNOX, D. L., and JENSON, A. D. (1973) *Arch. Ophthalm.*, **89**, 296
 VAN METRE, T. E. JR., and MAUMENEE, A. E. (1964) *Ibid.*, **71**, 314
 WILKINSON, C. P. (1976) *Amer. J. Ophthalm.*, **82**, 140
 WOODS, A. C., and WAHLEN, H. E. (1960) *Amer. J. Ophthalm.*, **49**, 205