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Ocular Histoplasmosis

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ABSTRACT

Case reports of three residents of Ontario with clinical histoplasmic chorioretinitis are presented. The diagnosis was made on the basis of the clinical appearance, the presence of calcified lesions in the chest, a negative skin test to tuberculin, and a positive skin test to toxoplasmin. All patients were treated with intravenous amphotericin B. Except for transitory elevation of blood urea nitrogen, there were no serious complications from the drug and in all cases the lesions in the eyes were improved. Histologic or cultural proof of the presence of fungus in the eye is not available, but clinical and laboratory findings can combine to point to the diagnosis of histoplasmosis. In such cases, since vision is at stake, treatment with amphotericin B should be considered.

INFECTION by *Histoplasma capsulatum*, which was a pathologic curiosity in 1945, is being reported with increasing frequency. The epidemiology has been discussed by others and attention has been drawn to the benign subclinical form of the infection.[1-3] While surveys involving humans, domestic animals and rodents have implicated the East-Central part of the United States as an epicentre of the disease,[4-6] a significant concentration in Canada was revealed in 1957, when Haggar, Brown and Toplack[7] reported seven fatal cases from southern Ontario. They presented the results of 400 histoplasmin skin tests performed on a random sample of the population in the St. Thomas, Ontario, area; the incidence of 79.3% positive skin reactors was unexpected. Canadian reports provide a general frame of reference but leave many gaps.[8-15] In this connection one should note the increasingly held opinion that cases of histoplasmosis occur in spot concentrations; in a region of endemic histoplasmosis there may be small areas where the fungus is particularly abundant, with corresponding concentrations of infection in the population.[16-19]

Against this background three cases of posterior uveitis in which *Histoplasma capsulatum* was the presumed agent are of interest. Since culture or biopsy from the eye is rarely possible, the triad of pulmonary calcification, a negative tuberculin skin test and a positive histoplasmin skin test are the main criteria for provisional diagnosis. A complement fixation test is available and is performed using both the yeast phase and histoplasmin as antigen. A titre of 1:8 or more suggests active disease.

CASE REPORTS

CASE 1.—A 46-year-old executive was seen in January 1958, complaining of decreasing vision in his right eye for one week. There was no pain, photophobia or other ocular symptoms. When he was 10 years old his left eye had been injured. An operation for traumatic cataract was unsuccessful and he retained vision in his right eye only. He was in the habit of having annual ocular examinations and his visual acuity had always been 20/20, without correction. In 1955 he noted slight blurring of vision, which subsided rapidly. The diagnosis at that time was "mild posterior uveitis not involving the central area". Investigation was limited to a skin test with old tuberculin (1/2000) which was negative.

His general medical history and functional enquiry were unrevealing. He was born in Toronto and has lived there all his life except for short holidays outside the city.

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Ocular Examination

Visual acuity in the right eye was 20/40 without correction; in the left eye there was no light perception. The anterior segments of the eyes were normal. The right fundus showed a reduced foveal reflex and a general haziness at the posterior pole. There was a small pigmented lesion in the upper nasal periphery. Just temporal to the disc were three small, round, pigmented scars and inferior to the disc a small white-yellow scar. All these lesions seemed old and quiescent. The whole macular area was swollen, with a diffuse crescent-shaped hemorrhage around it. The remainder of the fundus was normal. There was no scotoma to a 1.0-mm. white target at 1000 mm. but a paracentral scotoma was present to blue and red 2.0-mm. targets. The left eye was cataractous.

General physical examination revealed no abnormalities. White and red blood cell counts, serum calcium and blood sugar were normal. The erythrocyte sedimentation rate was 34 mm. per hour on admission and decreased to 15 mm. per hour after two weeks. Total blood proteins were 6.4 g. %, with an albumin level of 5.4 g. % and globulin of 1.0 g. Skin tests with old tuberculin (1/2000 and 1/1000) and toxoplasmin were negative, but with histoplasmin a strongly positive skin test was observed. Roentgenograms indicated several large and small calcified areas in the chest, particularly near the right hilum. This finding was interpreted as being compatible with old lesions due to histoplasmosis, with no evidence of active disease. A provisional diagnosis of active central chorioretinitis due to histoplasmosis was made.

Definitive treatment was not undertaken until July, when amphotericin B (Fungizone), 17.0 mg. per day intravenously, increasing to 50 mg. per day, was given

until a total of 1.175 g. had been administered over a period of 20 days. Sulfamethoxypyridazine (Kynex), 0.5 g. twice daily, and prednisolone, 5.0 mg. four times daily, were also given. Nitrogen retention did not occur. A hypersensitivity reaction on the third day was controlled with chlorpheniramine maleate (Chlortripolon).

Five weeks after admission, his treatments concluded, there was little change in the right fundus, except for a subsidence of the macular edema. Visual acuity in the right eye at that time was 20/30.

Gradually the swelling in the macular area decreased, the hemorrhage absorbed, the region took on a yellowish colour on its temporal side and a dark-brown colour on its nasal side. Visual acuity in the right eye improved to 20/20 without correction. This was his status in January 1963.

CASE 2.—In the autumn of 1958, a 41-year-old mechanic noticed a decrease of visual acuity, more of the left than of the right eye. He obtained glasses from an optometrist. In the spring of 1959 there was a further decrease of acuity of his right eye. He was found to have disseminated chorioretinitis with old lesions in the left eye and active lesions in the right eye. After taking corticosteroids by mouth for two months there was no improvement in his vision and he was unable to return to his job. In the spring of 1960 there was a further rapid decrease of vision in his left eye associated with a "black spot" in his sight and some blurring of vision in the right eye. Again corticosteroids were given for two months, without improvement. A third episode of decrease of vision in the right eye occurred in the fall of 1960 and it was at that time that the following studies were done.

He was born on a farm near Tillsonburg, Ontario, and worked on farms in the Tillsonburg—St. Thomas area until he moved to Sudbury in 1940, at the age of 20. He worked as a mechanic, underground, in the mines. During his vacations he usually spent two weeks with his relatives on their farm in southern Ontario. In 1956 he demolished an old barn at his place of residence in Sudbury. He described this as a dirty and dusty job. He could not remember any flu-like illness at that time but admitted that he may have forgotten such an event. On examination, visual acuity in the right eye was 20/200 without correction and 20/80 with correction. In the left eye, acuity was restricted to ability to count fingers at a distance of 2 feet, not improved by correction. There were no signs of inflammation in the eyes on external examination, or with the aid of the slit-lamp. The right fundus had many scattered yellow-white lesions in the periphery, showing various degrees of pigmentation. The macular area was swollen, with diffuse, fine, pigmented deposits. At its upper border were several thin scars, and more nasally was a lesion measuring one-half disc in diameter, with its lower pigmented border extending into the foveal region. Fine pigmentation was present between the macula and disc. The disc had sharp outlines and normal colour and texture but was surrounded by a ring of fine, dark pigment against a yellow background. There were no hemorrhages. The periphery and the disc of the left eye were similar in appearance to the right eye. At the macula, however, was an old, atrophic, yellow-white lesion exceeding the disc diameter in size and surrounded by fine mottled pigment.

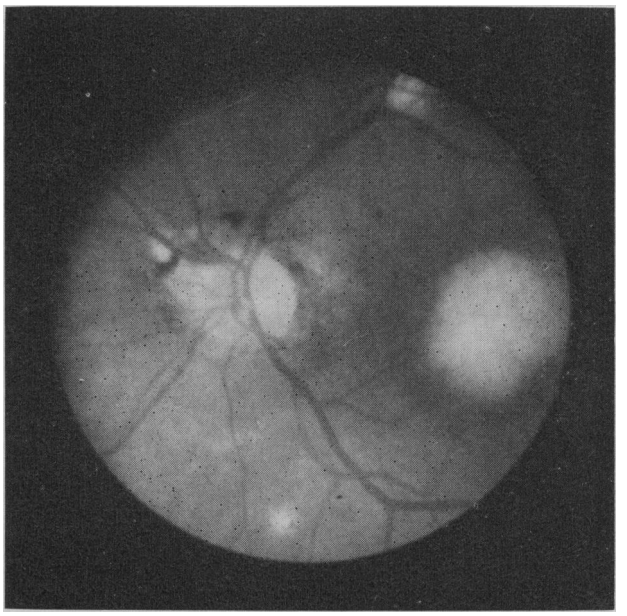

Fig. 1.—Case 2. Left eye showing an active lesion larger than the disc and involving the macular area. Smaller lesions are seen superiorly, inferiorly and at the disc margin.

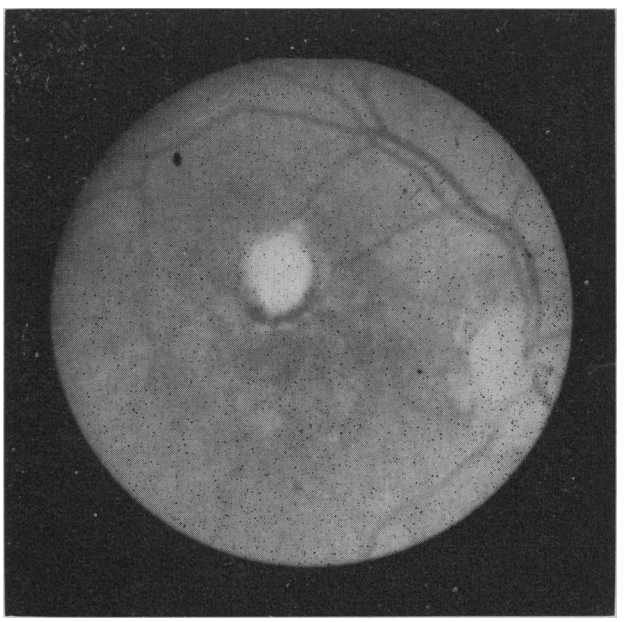

Fig. 2.—Case 2. Right eye showing a large active lesion at the macula. Edema and pigmentary changes are present throughout the macular area and around the disc.

There were no abnormalities on general physical examination.

The white blood cell count was 11,000 per c.mm., erythrocyte sedimentation rate 11 mm. per hour, and blood urea nitrogen 10 mg. %. Skin test with old tuberculin (1/2000) was negative, with toxoplasmin mildly positive, and with histoplasmin markedly positive. The Toxoplasma complement fixation test was negative. The Sabin-Feldman dye test for Toxoplasma was positive in a titre of 1:64. Blastomycosis and coccidiomycosis complement fixation tests were negative. The histoplasmosis complement fixation test was positive in a titre of 1:16; this was interpreted by the Kansas City Field Station (United States Public Health Service) as suggestive of active disease. A Kahn test was negative. Roentgenograms of the chest showed

multiple scattered calcific foci, predominantly in the lower two-thirds of both lungs, presenting an appearance compatible with histoplasmosis. A provisional clinical diagnosis of active central chorioretinitis due to histoplasmosis was made.

Treatment consisted of prednisone, 10 mg. every six hours, and amphotericin B (Fungizone). The latter was started with a dose of 20 mg. daily, given in 5% glucose in water, and was increased in increments of 10 mg. daily to a maximum daily dose of 100 mg. The treatment lasted 22 days. The blood urea nitrogen rose to a high of 45 mg. % on the eighth day and then gradually declined to 21 mg. % at the conclusion of treatment. The white blood cell count rose to a high of 17,000 per c.mm., probably owing to local thrombophlebitis. The erythrocyte sedimentation rate rose to 34 mm. per hour. The urinalysis remained within normal limits. A total of 1200 mg. of amphotericin B was given. The predisone dosage was gradually tapered off at the end of treatment. At the conclusion of treatment his visual acuity was 20/60 in the right eye, with correction, and 20/300 in the left eye, with a large central scotoma. There was marked reduction of the swelling and haze at the discs and in the macular areas. Particularly in the right fundus considerable clearing had occurred between the disc and the macula. In February 1963, his visual acuity with correction was 20/60 in the right eye and 20/300 in the left.

CASE 3.—In July 1962, a 32-year-old housewife complained of decrease of visual acuity in her right eye for six weeks, accompanied by a sensation of flashes of light. She had always enjoyed good vision and had no previous complaints referable to her eyes. She stated that she had had an attack of rheumatoid arthritis at the age of 18 years. Her residence had always been within 30 miles of metropolitan Toronto. At the age of 20 she had lived on a farm near Newmarket, Ontario, but was not involved in farm work. Since the age of 25 she had lived in a modern subdivision 20 miles north of Toronto. Except for a budgerigar that she kept in a cage, she denied any contact with wild birds, domestic fowl or animals and disclaimed any interest in gardening or other activities which would involve contact with soil. There was, however, a concentrated starling population around her house, particularly at the rear of the lot.

Visual acuity in the right eye was 20/60, unimproved by pin-hole or refraction, and in the left, 20/20 without correction. The anterior segments of both eyes were normal, and there was no flare or cells in the anterior chambers. In the right fundus, inferotemporal to the macula, was a raised lesion which extended into the lower macular area. This was yellow, edematous, and a third the size of the disc, with some fine pigment at its border. No other lesions were present and the disc and vessels were normal. The left fundus was normal. No abnormalities were found on physical examination.

Her white blood cell count was 6400 per c.mm. with a differential count of polymorphonuclear cells 64%, lymphocytes 25%, and bands 11%. The erythrocyte sedimentation rate was 41 mm. per hour. The level of total serum proteins was 7.2 g. %, with albumin 4.0 % and globulin 3.2 g. %. The blood urea nitrogen was 9.0 mg. %. Cutaneous reactions to tuberculin (1/2000), coccidioidin, and toxoplasmin were all negative. The reaction to histoplasmin was strongly positive within 24 hours, appearing as an erythematous area 3.0 cm. in diameter, with a central patch of induration. The Kahn test and the Feldman-Sabin test for Toxoplasma were negative. In the lungs, roentgenograms showed patchy infiltrative changes involving the anterior segment of the right upper lobe, with some pleural reaction in that area. These changes were suggestive of recent active granulomatous disease. A provisional diagnosis of active central chorioretinitis due to histoplasmosis was made.

The patient was given amphotericin B, 20 mg. per day increasing to 50 mg. per day, and hydrocortisone (Solucortef), 30-50 mg. daily, the dosage of the latter being gradually tapered off. A total of 1300 mg. of amphotericin B was given over a period of 33 days. The patient had chills on three occasions. The blood urea nitrogen rose to 26 mg. %, declining to 18 mg. % near the end of the treatment. After three weeks of treatment visual acuity of the right eye was 20/30. The edema at the area of choroiditis was less, and the lesion was smaller. In January 1963, the visual acuity of the right eye was 20/20.

DISCUSSION

Although estimates of the number of people infected by *Histoplasma capsulatum* have been continuously revised upward (according to some it may be as high as 30 million in the United States), ocular lesions due to this agent have not been common. The first report of ocular involvement was in a fatal case of human histoplasmosis described by Reid *et al.*[20] in 1942. The fundal lesions were described as "small, white, irregular areas surrounded by hemorrhage and not unlike tubercles". The patient was a 38-year-old Negro who showed evidence of the disease at autopsy. The eyes were not studied. A clinical and experimental study of ocular histoplasmosis was reported by Day[21] in 1949. His clinical series included 118 unselected cases seen at the Wilmer Eye Institute. Twenty-one had uveitis; of these, 14 (67%) had positive skin reactions. In the control group of subjects without uveitis, 30% had positive skin tests. Four of the group of 14 with uveitis and positive skin tests met the criterion of the clinical triad in that they had pulmonary calcification, a positive histoplasmin skin test and a negative tuberculin skin test. In none of the four was another cause for the uveitis found. Day followed the course of uveitis in rabbits after injection of the fungus into the anterior chamber, and found either a nodular iritis which subsided in four to six weeks, or a fulminating iritis leading to glaucoma. The largest series of cases was reported by Woods and Wahlen[22] in 1959. In accordance with Woods' criteria, 293 patients with uveitis were classified into 107 patients with non-granulomatous and 186 patients with granulomatous disease. The non-granulomatous group showed a positive histoplasmin skin reaction in 15%, whereas 33% of the granulomatous group had positive histoplasmin skin tests. This incidence among the granulomatous group is considerably higher than that found by Palmer in his general survey of normal persons (21%). Woods, making

TABLE I.—CLASSIFICATION OF GRANULOMATOUS UVEITIS

Group	X-ray	Skin tests			
		Old tuberculin	Histoplasmin	Toxoplasmin	
I	+	—	+	—	Considered histoplasmic
II	—	—	+	—	Considered histoplasmic
III	+	—	+	+	Here the complement fixation and the fundal appearance are aids in the diagnosis.
IV	+	+	+	—	The diagnosis lies between histoplasmosis and tuberculosis.
V	+	+	+	+	Course of the disease, results of blood tests, and evidence of systemic involvement may be of help.
VI	A miscellaneous group				

allowance for the varying incidence in different localities, stated that "the probability that the difference is due to chance is less than 0.01%". He suggested a classification into six groups indicated in Table I. This emphasizes the diagnostic dilemma, but the combination of serologic tests and certain characteristics in the fundus are the present diagnostic criteria for ocular involvement with this fungus.

While the fundal lesions show some variation, sufficient common features are found to permit a description of histoplasmic chorioretinitis. The lesions are discrete, atrophic, round to oval, yellowish, either unpigmented or sparsely pigmented and located from the midperiphery to the ora serrata. Prominent and cystic-appearing lesions occur at or near the macula. Woods reported an acute hemorrhage about a central lesion 24 hours after a diagnostic intracutaneous injection of histoplasmin.

Falls and Giles, in 1959, reported nine cases of chorioretinitis presumed to be due to histoplasmosis. In six, positive serologic findings and positive histoplasmin skin tests were present. All patients received amphotericin B in doses ranging from 0.5 to 1.0 g., and five received corticosteroids in addition. One year later, or when the lesions were quiescent, the visual acuity was either maintained or improved in seven eyes and decreased in five eyes.[23] Although the etiology was not proved and the treatment was not specific, owing to the adjuvant use of steroids, a cure rate of better than 50% can be considered high.

Case 1 belongs to Woods' Group I (Table I): In addition to the triad of a lesion in the chest, a positive skin test to histoplasmin, and a negative skin test to tuberculin, the patient had a negative toxoplasmin skin test. Another interesting feature is the time-lag of three years between a mild peripheral posterior uveitis and a paramacular cystic lesion with a crescent-shaped hemorrhage surrounding it. This patient thus exhibited the triad and two other clinical features which, apart from the therapeutic success with amphotericin B, support the presumptive diagnosis of histoplasmic chorioretinitis. The presence or absence of bilaterality could not be established, as the left eye had a cataract.

Case 2 fits into Woods' Group III (Table I): In addition to the aforementioned triad, the patient had a positive toxoplasmin skin test. The histoplasma complement fixation test suggested the presence of active disease, the titre being 1:8. This patient resided in northern Ontario for almost 20 years, and histoplasmosis is believed to be rare in the northern latitudes. His infection raises the question whether endemic foci exist in those latitudes (e.g. in the barn which the patient demolished) or whether he had been previously infected in southern Ontario.

In Case 3 there were no peripheral lesions. The lesion that was close to the macula did have a cystic appearance but there was no hemorrhagic reaction around it. The patient had a negative toxoplasmin skin test and fulfilled the criteria of the triad. Therapeutic confirmation is suggested by the subsidence of activity and improvement of visual acuity from 20/60 to 20/30.

SUMMARY

The three cases of ocular histoplasmosis are reported and a brief review of ocular histoplasmosis is presented, with special mention of Woods' classification of this form of the disease.

Ocular histoplasmosis represents but one aspect of systemic histoplasmosis but, because of its incapacitating consequences, demands treatment.

The evidence of ocular histoplasmosis is circumstantial: the organism has never been isolated from the eye, but sufficient clinical features are known to indicate a presumptive diagnosis.

Amphotericin B, in combination with steroids, seems to be the therapy of choice. The main contraindication to the use of this drug is impaired renal function. Frequent white blood cell counts and blood urea nitrogen determinations are mandatory in patients so treated.

Prompt diagnosis and therapy may result in the retention of good visual acuity.

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