SYSTEMIC HISTOPLASMOSIS IN SOUTH AFRICA

A REVIEW OF THE PREVIOUS CASES AND A REPORT OF AN ADDITIONAL CASE—THE FIRST SUCCESSFULLY TREATED

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The first case of systemic histoplasmosis in South Africa was reported by Simson and Barnetson in 1942,[1] and Murray and Brandt[2] reported 3 cases in 1951. In the following year 2 more were seen; one by Lurie and Brandt[3] and one by Dormer.[4]

There appear to be at least 4 clinical types of histoplasmosis: (1) the acute systemic infection involving the reticulo-endothelial system, (2) the benign pulmonary form, (3) the chronic pulmonary form, and (4) the localized ulcerated or gummatous lesion.

At least 3 South African cases[1,2] fall into the category of the acute systemic type. The benign pulmonary form is not infrequently seen as Cave disease.[5] Two cases possibly fall into the category of chronic pulmonary histoplasmosis. In the second case reported by Murray and Brandt[2] autopsy revealed marked interstitial fibrosis of the lungs which histologically suggested chronic tuberculosis, but no acid-fast bacilli or fungal elements were found. The patient investigated by Lurie and Brandt[3] had complained of a cough for 6 months. Physical examination of the chest showed poor air entry, and X-ray showed flattening of the diaphragm and obliteration of the costophrenic angles by adhesions owing to old healed pleurisy. There was a reticular pattern in both lung fields, especially in the upper zones. A lesion at the right apex was considered to be tuberculosis or possibly silicosis. The fourth type of histoplasmosis, viz. the localized ulcerated or gummatous lesion, has not yet been encountered in South Africa, although such cases have been seen in the Congo.

A summary of the South African cases is given in Table I.

REPORT OF PRESENT CASE

Mr. J.J.H., aged 49 years, production manager in a gramophone record factory. In April 1960 he began to feel out of sorts and suffered from insomnia and loss of appetite. He complained of sweating profusely and had lost a great deal of weight. He gave a history of having had pulmonary tuberculosis about 30 years previously, which was treated by pneumothorax. He was admitted to the Rietfontein Chest Hospital for investigation. When all tests for tuberculosis proved negative, he was transferred to the South Rand Hospital on 29 September 1960 for investigation of hepatosplenomegaly.

The only other relevant feature was a history of drinking heavily some years ago. He denied having explored caves, worked in dusty atmospheres or having kept chickens.

On examination the patient had obviously lost a great deal of weight. The cardiovascular system was normal and there was some diminution of air entry and scattered crepitations at the right base. The liver was enlarged to about 5 finger-breadths below the right costal margin and was tender. The

TABLE I. SUMMARY OF SOUTH AFRICAN CASES OF SYSTEMIC HISTOPLASMOSIS

Author	*Age*	*Sex*	*Race*	*Main symptoms and signs*	*Additional autopsy findings*	*Outcome*
Simson and Barnetson[1]	55	M	White	Ulcers on tongue, gums and lips. Enlarged cervical lymph glands.		Died
Murray and Brandt[2]	59	M	White	Ulcers on palate and lower lip.	Large ulcer posterior third of tongue, epiglottis destroyed, vocal cords involved. Ulcerations in colon.	Died
	64	M	White	Tongue swollen and painful with superficial ulcerations.	Lungs showed interstitial fibrosis and histological features of chronic tuberculosis (ZN-ve). Caseous necrosis of right suprarenal. Liver enlarged, histologically early perilobular fibrosis and small foci of reticulo-endothelial reaction with follicle formation and occasional giant cells. Spleen enlarged, histologically fibrosis of pulp and scanty reticulo-endothelial cells bordered by giant cells and showing central necrosis.	Died
	13	M	White	Enlarged cervical, supraclavicular and axillary glands. Spleen slightly enlarged.	Sections of spleen, lungs, intestine and lymph nodes showed collections of epithelioid cells and giant cells.	Died
Lurie and Brandt[3]	70	M	White	Ulcers on tonsils, palate and upper lip. X-ray of chest showed old healed pleurisy, reticular pattern in both lung fields, and a lesion at the right apex.		?
Present case	49	M	White	Hepatosplenomegaly. Ulceration of gum and cheek. X-ray of chest showed thickening and calcification of the pleura and an opacity at the left apex.		Cured

spleen was enlarged, but no lymphatic glandular enlargement could be felt.

Routine investigations revealed a very slight neutrophilia (75% of a total white-cell count of 9,400 per c.mm.) Bone-marrow studies showed a mild hyperplasia with the number of plasma cells at the upper limit of normal. The sedimentation rate was 2 mm. in one hour. The liver-function tests indicated some derangement; significant results were as follows:

Total protein 8 G %. Albumin 4 G. Globulin 4 G.
Alkaline phosphatase 56 King-Armstrong units.
Takata-ara reaction + positive.

Other laboratory investigations included:

Protein-bound iodine (5 October 1960) 8·3 micrograms per 100 ml.
Protein-bound iodine (26 October 1960) 10·5 micrograms per 100 ml.
Basal metabolic rate (8 October 1960) + 63
Basal metabolic rate (11 October 1960) + 41
Radioactive iodine uptake 37%
Thyroid suppression test 10%
Thyroid auto-antibodies present.

X-ray of the chest showed thickening and calcification of the pleura, probably the result of the previous pneumothorax; an opacity at the left apex suggested old healed tuberculosis. A needle biopsy of the liver was performed on 28 October 1960. Histological examination revealed the presence of increased fibrosis of the portal tracts with some focal fatty change. In addition there were several granulomata consisting of aggregations of epithelioid cells surrounded by a few lymphocytes, neutrophils and an occasional eosinophil. Some granulomata also contained multinucleated giant cells (Fig. 1). Although acid-fast bacilli were not observed in suitably

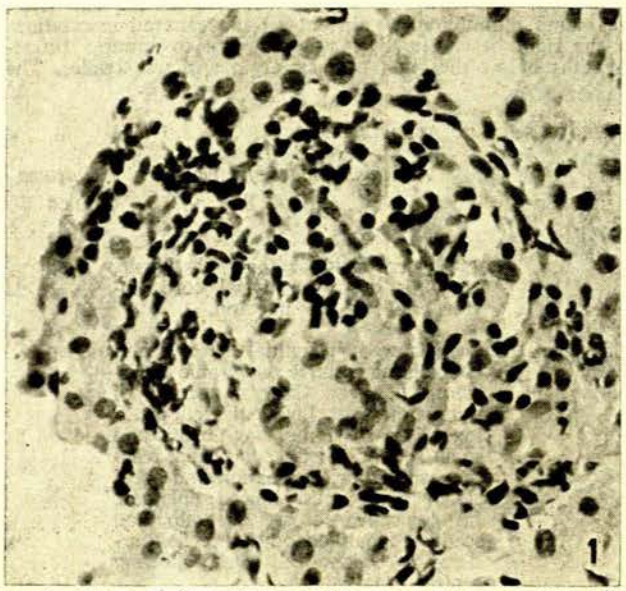

Fig. 1. Section of liver biopsy showing granulomata and giant cells. H. & E. x 480.

stained preparations, the features were considered to be consistent with those of tuberculosis.

On the basis of these findings the patient was given antituberculous therapy with some slight improvement in his condition. At this stage he developed a small ulcer in the mouth which was thought to be due to badly fitting dentures. On 11 November 1960 he was discharged from hospital with instructions to report regularly at the outpatient department.

When next seen his main complaint was that the ulcer on his gum was not healing, and in fact was spreading. By mid-December there was a large necrotic area in the mouth with extension on to the cheek. The angle of the jaw was swollen and erythematous and, since there was suspicion of underlying osteitis, the mandible was X-rayed. However, no evidence of bone involvement was detected. The gum lesion was biopsied and histological examination revealed the presence of histoplasmosis (Fig. 2). The previous liver biopsy

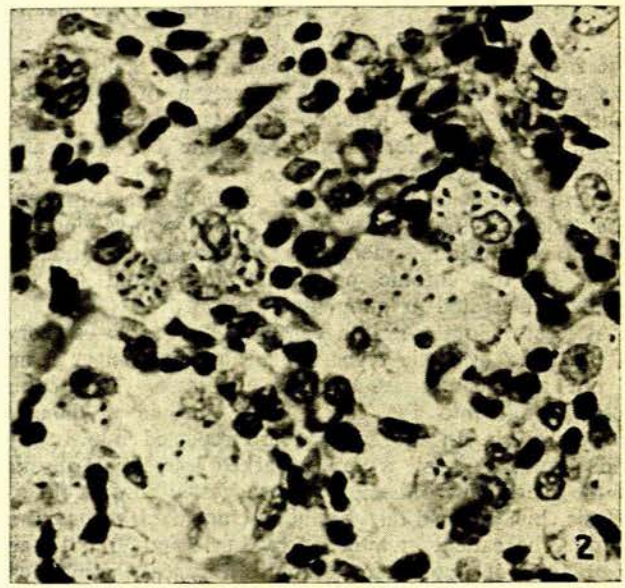

Fig. 2. Section of biopsy from gum showing numerous intracellular yeast-like organisms. P.A.S. x750.

sections were reviewed and further sections were stained with the periodic-acid-Schiff stain. No yeast-like bodies were detected in the granulomata, giant cells or Kupffer cells. However, it was felt that the lesions in the liver were consistent with a diagnosis of histoplasmosis.

Cultures of material obtained from the ulcer of the gum resulted in the growth of *Histoplasma capsulatum*. The histoplasmin skin test and complement fixation test gave negative results.

The patient was readmitted to hospital on 28 December 1960 for amphotericin B treatment ('fungizone'). The initial dose was 12½ mg. per day administered by intravenous drip. The dose was increased daily or on alternate days, depending on the reaction, until he was getting 35 mg. per day. The reactions consisted of rigors, headaches and general aches which he described as feeling as though he had been bruised all over. A total of 400 mg. of fungizone was given over a period of 20 days.

There was some improvement and the gums started to heal, but on 11 February 1961 the gum became painful again and, since the patient was not feeling well, it was felt that the treatment had been inadequate. A further course of fungizone was given, starting with 15 mg. per day and increasing the dose every 2 or 3 days until he was receiving 50 mg. per day. A further 990 mg. was given over a period of 33 days. Each dose was accompanied by reactions which were reduced, however, by mixing 50 mg. of 'phenergan' with the infusion. The reason for starting at a low dose again was that there have been reports[6] of anaphylactic reactions resulting from stopping and restarting administration of the drug, and in fact hydrocortisone was kept in readiness at the bedside. As amphotericin B is toxic to the liver, kidneys, and bone marrow, liver-function tests, blood-urea estimations and blood counts were done repeatedly. The liver-function tests remained unaltered, except for the alkaline phosphatase which rose to 70 King-Armstrong units; the blood urea rose to 57 mg. per 100 ml., but the blood count remained static.

The only other reaction of interest was the development of a phlebitis whenever a 'new' vein was used; it was almost as

though repeated use of the same vein 'habituated' it to the passage of the solution.

The patient was discharged on 16 March 1961, feeling well. He has been seen by one of us (H.B.K.) on a number of occasions since then; he has gained about 50 lb. in weight and in fact he is now on a reducing diet; his blood urea has returned to normal. The alkaline phosphatase was still raised in November (44 King-Armstrong units). The liver and spleen, though still palpable, seemed to be somewhat smaller and softer.

Comments

The majority of the clinical findings were in keeping with the diagnosis of histoplasmosis. Possibly the old alcoholic imbibition contributed to the hepatomegaly. The finding of thyroid auto-antibodies may be due to a coincident thyroiditis without incriminating the histoplasmosis.

SUMMARY

A case of chronic systemic histoplasmosis with an acute exacerbation is described. The patient was successfully treated with amphotericin B (fungizone). This is the seventh case of systemic histoplasmosis in South Africa. The previous 6 cases are briefly reviewed.

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