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DISSEMINATED HISTOPLASMOSIS AND ITS TREATMENT

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DISSEMINATED histoplasmosis is the most serious form of the disease produced by the fungus *Histoplasma capsulatum*. Only five cases of this type have been reported in Britain (Derry, Card, Wilson, and Duncan, 1942; Lockey, Atkinson, Grieve, and Bridson, 1953; Poles and Lavertine, 1954; Earle, Highman, and Lockey, 1960; Miller, Ramsden and Geake, 1961).

Histoplasmosis, first described by Darling in 1906, is common in N. America and Asia. Patients seen with histoplasmosis in this country have usually contracted the disease abroad; endemic infection is rare (Symmers, 1956). This paper describes a case of disseminated histoplasmosis, probably contracted in Malaya, and its successful treatment with amphotericin B.

Case Report

Mrs. J. M., an Englishwoman, aged 42, lived in Malaya for nine years, with brief visits to India and Ceylon. During her sojourn, she experienced several bouts of fever of unknown origin, the last attack in 1959 necessitating hospital treatment. Later in 1959, a three month trip in the U.S.A., from Washington through Alabama and Tennessee to Los Angeles and San Francisco, was followed by visits to Japan, Hawaii and Hong Kong. Afterwards she returned to England.

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In February 1961 she developed a dental abscess. The tooth was extracted and an upper plate fitted. This was followed by gingivitis and formation of white 'spots' on the back of her tongue and throat. A month later she developed nocturnal pyrexia with sweating, accompanied by increasing lethargy and slight dyspnoea on exertion. By November she had lost 28 lbs. in weight.

On admission to King's College Hospital (27.11.61.) examination revealed a palpable spleen, enlarged two inches below the costal margin, and a pelvic swelling later shown to be due to uterine fibroids. Chest X-ray normal. A blood count showed a mild iron deficiency anaemia; Hb 11.6g./100ml.; WBC 11,000/cu. mm., normal differential; ESR 8mm./hr. (Westergren). Wasserman test gave an intermediate reaction and the Kahn test was positive.

No definite diagnosis was made at this stage, but during the next two months she developed increasing dysphagia and hoarseness; white 'spots' had again formed in her mouth. Laryngoscopy revealed a granular appearance of the posterior hypopharyngeal wall with keratotic changes of both vocal cords, particularly the left, and some ulceration; full mobility of the vocal cords was retained. Pallor and papillar hypertrophy of mucosa over the arytenoids were suggestive but not typical of tuberculosis.

Biopsy material from interarytenoid and subglottic regions (25.1.62.) showed no histological evidence of tuberculosis and no micro-organisms were seen. *M. tuberculosis* was not grown from biopsy tissue, blood or sputum. (Streptomycin, PAS and INAH were given pending further investigation.)

By March, 1962, adrenal suppression was suggested by a low plasma sodium, 116 mEq/l, and the ESR was 40mm./hr. (Westergren). Her voice was a whisper and laryngoscopy showed an increase in size of the interarytenoid area with further ulceration. A biopsy was taken (15.3.62.) and histological examination showed the connective tissue to be heavily infiltrated by inflammatory cells, the chief cell being a reticulo-endothelial cell containing small yeast-like bodies resembling *Histoplasma capsulatum* (Fig. 1). However, as well as the cells that resembled the usual tissue form of this organism there were also ovoid, cyst-like structures that each contained several fungal cells in a clear matrix. These cyst-like forms were of the type observed by Symmers (1964) in cases of histoplasmosis acquired in Asia (see Discussion, below).

The spleen was considerably larger and the liver enlarged and soft. No micro-organisms were seen in sections of liver biopsy material (21.3.62.) the tissues showing normal architecture.

Diagnosis of histoplasmosis was confirmed by the isolation of *Histoplasma capsulatum* from both the liver biopsy (2 colonies only) and the laryngeal biopsy; there was also a heavy yield of *Candida albicans* from the latter.

The histoplasmin complement fixation test (CFT) was strongly positive and gave a maximum titre of 1/512 (see Fig. 3); the skin test was negative. Sensitivity tests to amphotericin B and M & B 938 showed inhibition of the organism at levels of 0.3µg. and 2.5µg./ml. in peptone-dextrose water (0.5 per cent concentration; pH 7).

Treatment. Because of the prolonged course of the disease in this patient, treatment will be presented in three sections, corresponding with admission to hospital.

(1) Amphotericin B was given intravenously, the maximum dose tolerated being 30 mg. Despite the use of anti-histamines, infusion of the drug caused toxic reactions with severe local cellulitis and rigors. Over a period of two months (27.3.62. - 21.5.62.) a total of 535 mg. of amphotericin B was administered. Cortisone

FIG. 1.—Laryngeal biopsy (15.3.62). Stained: haematoxylin and eosin; $\times$ 290. (photographed by Mr. A. Campbell, C.X.H.).

was given because there was thought to be adrenal suppression.

During treatment the plasma potassium fell to 2.8 mEq/l. but was corrected with oral potassium chloride. The haemoglobin was 9.7 g./100 ml. and three pints of blood were transfused. In spite of the severe reactions the patient showed great improvement. The throat condition cleared and the spleen was considerably reduced in size by the end of May. The histoplasmin CFT gave a titre of 1/20 and the histoplasmin skin test was positive.

She was discharged and continued hospital attendance as an out-patient from 26th June, 1962. By mid-July, the histoplasmin CFT titre was 1/5, but in August the laryngitis recurred following two 'colds'; the spleen remained palpable and the pelvic tumour was bigger. The rise in the titre of the histoplasmin CFT to 1/80 in September (4.9.62.) confirmed the likelihood of a relapse.

(2) The patient was readmitted to hospital in October, 1962, for a further course of treatment. At this stage the vocal cords appeared somewhat thickened, but no ulceration was seen. The arytenoid area was slightly oedematous with some ulceration and another biopsy was taken. Although chronic inflammatory cells were visible in section, no organisms were seen and cultures were negative for histoplasma.

Amphotericin B was again given intravenously. The initial dose was 0.5 mg., this being slowly increased until 50 mg. could be tolerated when given approximately every 2-3 days. This level was maintained until 25.1.63., when a total of 2,300 mg. amphotericin B had been administered. For this course of treatment the antibiotic was diluted with Seitz-filtered 5% dextrose. There were no troublesome reactions.

Titres of the histoplasmin CFT during this course of therapy fluctuated between 1/20 and 1/80. By January, 1963, her laryngeal condition had improved and only a trace of thickening in the interarytenoid region was seen. The spleen was still easily palpable, and the pelvic tumour was hard and mobile. She was discharged and continued out-patient attendance from 5th February, 1963.

Despite three 'colds', she remained relatively well but tired easily; the spleen remained enlarged. However, by the end of April the histoplasmin CFT titre was 1/160.

(3) She was admitted for another course of treatment in May, 1963, and for laparotomy. Amphotericin B was given, the dose being increased rapidly from 2 to

FIG. 2.—Subphrenic abscess wall (11.6.63). Stained : methenamine silver ; $\times$ 590 (photographed by Mr. G. Harwood, K.C.H.).

50 mg. and continued for several days at this level before and after operation.

Laparotomy was performed on 11th June, 1963. A subphrenic abscess was discovered, with the spleen incorporated in its wall. The spleen was mobilised and removed, and the abscess cavity drained of approximately two ounces of green pus. The pelvic mass was found to consist of uterine fibromyomata which were not removed.

Histological studies of the spleen revealed considerable reactive changes and an increase of fibrous tissue; no

organisms were detected. The abscess wall showed several small necrotic cellular foci in which numbers of histoplasma-like bodies were found. These showed little nuclear staining with haematoxylin, but large numbers were detected with specific staining, particularly with Gomori's methenamine-silver technique, indicating a relatively non-active or old infection (Fig. 2). Cultures of the spleen abscess wall and pus were negative for *H. capsulatum*.

She was discharged and continued out-patient attendance from 26th June, 1963. The titre of the histoplasmin CFT at this time was 1/40. From August to December, 1963, titres of the CFT remained at a level of 1/20. She was admitted in April, 1964, for removal of her lower teeth. Cultures of extracted teeth were negative for histoplasma. The titre of her histoplasmin CFT on this last occasion was negative.

She has since remained well and regained her original weight, but continues to take 37.5 mg. cortisone and 0.1mg. fludrocortisone daily. She now 'feels better than she has done for years.'

Discussion

Source of infection. Although the patient travelled through the southern states of the U.S.A. which are endemic for histoplasmosis, it is more likely that she contracted the infection during her stay in Malaya. She did not visit the Batu caves, famous for their bat colonies and incidentally a possible source of *H. capsulatum* (Ponnampalam, 1963). However, bats are very prevalent in the eaves of many Malayan homes.

FIG. 3.—Histoplasmin complement fixation titres.

with their droppings frequently being scattered into the living quarters, and it is possible that this nitrogenous material, together with the hot humid climate, provides a suitable environment for growth of the fungus and a source of infection. Cases of human histoplasmosis have been reported in Malaya, and skin testing of patients attending a chest clinic are suggestive of a high incidence of the infection amongst the population (Ponnampalam, 1964).

Clinical manifestations. It is possible that the bouts of fever experienced by this patient when in Malaya were indicative of early infection. In view of the presence in the laryngeal biopsy specimen of the cyst-like form of the parasite that Symmers considered might be peculiar to histoplasmic infections acquired in Asia, it is of interest that our patient presented both the main clinical features that he regards as characteristic of a large proportion of the cases of 'Asian histoplasmosis' recognised in Britain among former expatriates. These features are very painful mucosal or mucocutaneous ulcers and serious adrenal involvement. It must be stressed that Symmer's suggestion that there may be a distinct species, *Histoplasma asiaticum*, has not yet been confirmed. Fever, mucomembranous lesions and splenomegaly are typical of all types of disseminated histoplasmosis. The adrenal glands are frequently involved, as seen at necropsy (Parsons and Zarafonetis, 1945; Crispell, Parson, Hamlin and Hollifield, 1956). In one case sudden death occurred without clinical signs of adrenal involvement, although both adrenals were found to be grossly damaged at necropsy (Lockey, Atkinson, Grieve and Bridson, 1953). Our patient had hypotension and a low plasma sodium, and later was unable to respond to ACTH. The sub-phrenic abscess may have arisen from the left adrenal.

Treatment. Amphotericin B is the drug which so far has proved most successful in treatment of disseminated histoplasmosis, but it is also a drug of considerable toxicity. Furcolow (1963) reported 3 deaths after treatment of 11 patients with less than 25 mg. amphotericin B per Kg. body weight, and 2 deaths among 11 patients treated with more than this dose. Our patient received 2,300 mg. (41 mg./Kg.) during the second course of treatment, and a total of 3,137 mg. amphotericin B. Fevers and rigors are said to be common, (Seabury and Dascomb, 1958), but peripheral neuritis, respiratory muscle paralysis (Haber and Joseph, 1962), bone marrow depression, anaphylactic shock and ventricular fibrillation may also occur. Renal tubular damage has also been reported as a long term effect (Bell, Andriole, Sabesin and Utz, 1962).

There is no doubt that many of the reactions are due to the insolubility of amphotericin B and its precipitation with changes of pH. Experience in the first course of treatment given this patient emphasised the need for administration of the drug in a 5 per cent glucose solution, sterilised by Seitz-filtration to avoid lowering of pH. Local toxic reaction was greatly diminished by this procedure. Heparin may reduce local thrombosis (Winn, 1959) and hydrocortisone is reported to minimise general reactions (Seabury and Dascomb, 1958; Saliba and Beatty, 1962; Tynes, Utz, Bennett and Alling, 1963).

Splenectomy. Laparotomy was undertaken primarily to ascertain the nature of the pelvic mass, and splenectomy was performed because it was thought that the spleen might be acting as a reservoir of infection. The sub-phrenic abscess was an unexpected finding, and may have arisen from adrenal involvement. Although the abscess wall contained many yeast forms, all cultures were sterile owing to the patient receiving amphotericin B at the time.

It is doubtful how much the patient benefited from splenectomy, but removal of the abscess presumably removed a focus of infection which had prevented satisfactory recovery. After operation the histoplasmin titre steadied at 1/20, and was recorded as negative five months later.

Summary

The case of systemic histoplasmosis described presented with symptoms associated with progressive infection, i.e. splenomegaly, fever and mucocutaneous lesions, diagnosis being confirmed by isolation of the fungus from the tissues and serological tests.

Many people have been involved in the diagnosis and treatment of this case. In particular, we would like to thank Dr. I. G. Murray (Mycological Reference Laboratory, London School of Hygiene and Tropical Medicine) for the serological tests; Dr. R. S. Bruce Pearson (Medicine), Mr. R. S. Lewis (E.N.T.), Mr. A. J. Heriot (Surgery), Dr. B. S. Cardell (Morbid Anatomy), Professor A. C. Cunliffe (Bacteriology) and members of their departments at King's College Hospital. Also Professor W. St. C. Symmers (Charing Cross Hospital Medical School) for helpful advice and for contributions to this paper.

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HYPOGONADISM AND LIFE-LONG ANOSMIA

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THE association of life-long anosmia with gonadal failure in males was first described by Kallman, Schoenfeld and Barrera (1944) and reviewed by Nowakowski and Lenz (1961). The hypogonadism, which may be familial, is thought to be the result of pituitary failure because the urinary excretion of gonadotrophins is absent or greatly reduced, but there has been no indication of failure of secretion of pituitary hormones other than the gonadotrophins. de Morsier (1955) has reviewed the occurrence of agenesis of the olfactory bulbs and tract as found on post-mortem examination, usually of patients who were not known by their relatives to have had a defective sense of smell. Some of these patients were eunuchoid and in a very few the pituitary fossa was small. No evidence of adrenal or thyroid failure was recorded at post-mortem. In one child there was an absence bilaterally of neurones from the area usually occupied by the cells of the lateral tuberal nucleus of the hypothalamus. Damage to this region has been associated in animals with impairment of gonadotrophin production (Mess, 1952; Davidson, Contropoulos and Ganong, 1960).

Two patients are described who illustrate this association of life-long anosmia in males with hypogonadism secondary to pituitary dysfunction.

Case No. 1.

Mr. H. B. (Radcliffe Infirmary No. 303741) is a 27 year-old man who first attended Out Patients when aged 22 with the complaint of an abnormally high-pitched voice. Enquiry revealed many symptoms of reduced testicular function: he did not need to shave, was weak, and had ready "burning" of the skin without tanning on exposure to the sun, a lack of libido and of self-confidence, and only occasional erections. There was no similar abnormality among his family (he has one brother and one sister, both of whom are well, as are his parents). He had had no notable past illness or

operation, and had no history of mumps, as far as he remembered. He had had no headaches except occasional ones of the "tension" type. Vision was normal.

He had first complained to his practitioner of similar symptoms when aged 18, and had been treated with testosterone, both as the propionate ester parenterally and as methyl testosterone orally, for a short period. He had noticed changes of maturation on this treatment, with some deepening of his voice, scant growth of facial and pubic hair, and some penile enlargement. His abdominal and upper limb fat had decreased, while his appetite had, if anything, increased.

The results of physical examination were affected by the previous treatment with testosterone but the patient was clearly eunuchoid. Height was 70ins with span 72 and distance from floor to pubis 37ins. There was plentiful subcutaneous fat of feminine distribution over the hips, abdomen, upper parts of the limbs, and in the breasts (where no glandular tissue could be felt). Weight fluctuated between 10 and 11st. Scalp hair was fine in texture with little temporal recession. There was scant facial and pubic hair, and no axillary hair. The skin was pale and thin. The penis and testes were small but not infantile. Muscular strength was normal. The larynx was small but again larger than the usual pre-pubertal size.

Investigation at age 23 showed a normal haemoglobin, blood urea, sugar and electrolytes, while skull X-ray showed a small pituitary fossa with large frontal and maxillary sinuses. The chromosomal pattern of white blood cells was normal. Testicular biopsy revealed almost complete absence of Leydig cells with a reduced number of seminiferous tubules. The basement membrane of these was normal, but spermatogenesis was markedly abnormal, although spermatogonia and primary spermatocytes could be recognised. No spermatozoa were seen and no normal spermatids or secondary spermatocytes were present. The 24-hour urinary excretion of 17-hydroxy-corticoids was 10.2 mg. and of 17-ketosteroids 4.8 mg. Later (when age 28) no urinary gonadotrophins could be detected after extraction of the