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Oto-laryngeal histoplasmosis

by

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Introduction

Mucocutaneous localized histoplasmosis of the upper respiratory tract is rare and only a few cases have been reported, in spite of large numbers of systemic histoplasmosis found in endemic areas. Histoplasmosis was first described by Darling, who found three cases in 1905 and 1906, and twenty years passed until the fourth case was described by Riley and Watson in 1926 (cited by Parsons and Zarafonetis, 1945). Histoplasmosis is essentially a systemic disease, involving mainly the lungs, but other organs may also be involved. The otyolaryngologist should be aware of the existence of histoplasmosis in the upper respiratory tract, and of its ability to simulate tuberculosis, syphilis, carcinoma or any granulomatous lesion. Three cases of localized upper respiratory tract histoplasmosis are described, one in the tongue, one in the vallecula and the third case in the tonsil.

Case reports

Case 1

A 60-year-old white male presented with a three-month history of sore throat. He was seen by numerous general practitioners and received a number of courses of antibiotics, with no improvement. Eventually he was referred to an ENT specialist who performed an examination under anaesthesia (EUA). An ulcer of the vallecula was found and a provisional diagnosis of carcinoma was made. A biopsy of the ulcer was reported as non-specific ulceration. The patient was then referred to Addington Hospital where a repeat EUA and biopsy was performed. The ulcer of the vallecula extended onto the lingual surface of the epiglottis and onto the base of the tongue with underlying and surrounding induration. A number of biopsies were submitted for histology. The specimens all revealed the presence of an ulcerative granulomatous inflammation and numerous epithelioid cells containing multiple organisms morphologically resembling histoplasma. Physical examination of the patient revealed a well-looking, apyrexial patient, with no palpable cervical lymph nodes. An X-ray of the chest revealed an ill-defined patchy opacification involving both mid and upper zones, compatible with pulmonary histoplasmosis. Sputum culture was negative.

The abnormal investigations are listed: Alkaline Phosphatase 152 i.u., Gamma-GT 57 i.u., Serum Creatinine 113 mmol/l., Glomerular filtration rate 75 per cent of normal, Erythrocyte Sedimentation rate 25 mm./hr., White Blood Cell Count 3.1, Haemoglobin 13.0, Neutrophils 48 per cent, Lymphocytes 40 per cent, Monocytes nine per cent, Eosinophils two per cent, Band Forms one per cent.

Treatment with Amphotericin B was commenced, but the patient developed an anaphylactic reaction. The treatment was therefore subsequently changed to Micronazole 500 mg. i.v., three times a day, for four weeks. The ulcer in the vallecula responded well and cleared completely on this treatment. The radiological appearance of the chest

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X-ray improved slightly. He was discharged symptomatically much improved.

Case 2

A 56-year-old white male, first diagnosed as histoplasmosis in 1980 when he developed a tooth abscess. The tooth was extracted and a gum biopsy revealed histoplasmosis.

In January 1981, he was hospitalized with symptoms of tiredness, loss of weight, night sweats and sore throat. An examination under general anaesthesia revealed a mouse-eaten appearance of his epiglottis, a biopsy of which was diagnosed as histoplasmosis. The patient was transferred to Addington Hospital where he was noted to be wasted and pyrexial (38°C). He was treated with Amphotericin B which caused bone marrow depression. The treatment was changed to intravenous Miconazole 600 mg. twice a day. He improved on this treatment, gaining 4 kg. in weight. The lesions on both the gum and the epiglottis disappeared. Haematologic and liver indices returned to normal. After one month of treatment he was discharged to be followed up as an outpatient.

In July 1982, he was readmitted with lethargy, loss of weight, intermittent fever and some ulceration of the skin of the nose. A biopsy of the nasal lesion revealed histoplasmosis. A bone marrow aspirate did not reveal any fungal elements. X-ray of the chest was clear. Isotope scan revealed the presence of an enlarged liver and spleen. Liver function tests were abnormal: Total Serum Bilirubin 21.7 mmol/l., Conjugated Serum Bilirubin 6.1 mmol/l., Serum Alkaline Phosphatase 470 i.u., Glutamic Dehydrogenase 10 i.u., Aspartate Transaminase 65 i.u. A liver biopsy revealed a chronic granulomatous lesion with non-caseating tuberculoid granulomata consistent with histoplasmosis.

He was treated with Ketokonazole 400 mg. daily. Liver function tests on discharge: Alkaline Phosphatase 482 i.u., Bilirubin 18 mmol/l., Albumin 26 g./l, Gamma-GT 154 i.u., Aspartate Transaminase 42 i.u., Prothrombin Index 98 per cent. The Erythrocyte Sedimentation Rate was 12 mm./hour. He was maintained on Ketokonazole from July to December 1982. In September and October 1982, repeat liver function tests showed definite improvement.

In January 1983, he was readmitted with a history of irregular temperature over the preceding few weeks. He was found to have a swinging temperature. A liver biopsy was taken. Following this, he developed a fatal intra-peritoneal haemorrhage and haematemesis. Histology of the liver biopsy was in keeping with a histoplasmosis although no organisms were found. A medico-legal post-mortem was performed and the presence of histoplasma in the liver and spleen was confirmed histologically.

Case 3

A 64-year-old Indian male presented with a history of sore throat for three weeks. He had been treated by his physician with Ampicillin, 500 mg. four times a day for one week, with no improvement. The patient gave a history of hypertension which was well controlled on Aldomet 250 mg. twice a day.

On examination the vital signs were: blood pressure 170/80, regular pulse of 84 per minute and a temperature of 36.8°C. There was a 0.5 cm. ulcer on the left tonsil and no cervical lymphadenopathy or hepatosplenomegaly was detected.

A grade 2/6 systolic murmur was heard at the apex of the heart and the lung fields were clear.

The blood results showed a full blood count, urea and electrolytes to be within normal limits, and a negative VDRL. The chest X-ray was normal. The histology from a punch biopsy of the left tonsil showed histoplasmosis.

The patient was treated with Ketokonazole for two weeks with marked improvement, the tonsillar ulcer decreasing in size to a pinpoint lesion. He was then lost to follow-up for ten months and on returning, complained of a hoarse voice and sore mouth.

On examination, multiple nodular lesions could be seen on the buccal mucosa, spreading into the hypopharynx and larynx (Fig. 1). Chest X-ray showed bilateral hilar lymphadenopathy and right lower lobe infiltration.

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FIG. 1
Multiple histoplasmatic nodular lesions on the hard palate (Case 3).

A repeat biopsy of the mucosal lesion revealed histoplasmosis. A diagnosis of disseminated histoplasmosis was made and intravenous doses of Amphotericin B 30 mg. daily, increasing to 2 gm. were given for six weeks.

Discussion

Histoplasmosis is essentially a systemic disease involving primarily the lungs and is characterized by fever, cough, chest pain, chills, sweats, loss of weight, hepatosplenomegaly and lymphadenopathy. The presenting lesion may be localized to the upper respiratory tract. Usually, these patients subsequently develop more widespread or generalized infection which may involve the lungs, spleen, liver, lymph nodes, kidney, prostate, heart, brain, larynx, ear, nose, buccal mucosa, eye, bone, bone marrow or penis (Moore and Jordstand, 1943). Unusual manifestations such as parotitis, adrenal insufficiency, uveitis, interstitial nephritis, intestinal lymphangitis and epididymitis have been described (Wheat *et al.*, 1981). The disease may be acute or chronic, lasting for weeks or years. It may vary from a mild asymptomatic infection to a severe illness with a fatal termination. It may be classified according to Furcolow (cited by Schwartz, 1981) (Table I) as follows:

TABLE I
CLASSIFICATION OF HISTOPLASMOSIS: FURCOLOW

Acute pulmonary histoplasmosis
asymptomatic
symptomatic—mild
—moderately severe
—severe (acute epidemic)
Chronic pulmonary histoplasmosis
progrossive cavitary
Acute disseminated histoplasmosis
benign
progressive
Chronic disseminated histoplasmosis
mucocutaneous

Localized otolaryngeal histoplasmosis in this classification falls into the mucocutaneous group which is a chronic disseminated infection; however, it is possible that some localized cases may not be disseminated at the time of presentation (as in Case 3).

Young persons between the ages of 15–35 years are predisposed to the systemic disease (Whea *et al.*, 1981). The histoplasma skin test was positive in 55 per cent of white Indianapolis military recruits between 17 and 21 years of age (Edwards *et al.*, 1969). Serological testing in 1,280 juniors and seniors from 16 Indianapolis high schools resulted in findings of previous histoplasmosis infection in 17 per cent (Gunby, 1979). Otolaryngeal histoplasmosis, on the other hand, appears to have a higher incidence in older patients and 85 per cent of the 53 cases of the upper respiratory tract, reported in the literature, were above the age of 40 (Bennet, 1967). The patients presented in this article were all over the age of 50. Outbreaks of histoplasmosis may begin explosively after a common exposure to cleaning a chicken coop or a bird roost or demolishing an old building. In spite of the large number of persons estimated to acquire histoplasmosis each year, localized otolaryngeal histoplasmosis is rare.

Bennet (1967) reviewed 53 cases in which the presenting manifestation was histoplasmosis of the oral mucosa and larynx. Since then further cases have been described: a laryngeal case (Lierle and Carr, 1951), tongue

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histoplasmosis (Hiley *et al.*, 1967), eight ear cases (Parsons and Zarafonetis, 1945), four cases of nasal histoplasmosis (Curtis and Grekin, 1947), and these, together with the three cases presented in this paper, make a total of 70, an insignificant number with respect to the relatively high incidence of systemic histoplasmosis. The larynx and the tongue are the sites of predilection. Clinially, the localized lesion presents as an ulcer or a nodule, but occasionally as a verrucous or granular mass. It may appear polypoid, necrotic or oedematous. The lesions are usually misdiagnosed as tuberculosis, syphilis or carcinoma. Mucocutaneous leishmaniasis closely resembles histoplasmosis and can be mistaken for this disease. Culture was not performed as a granulomatous infection was not suspected.

Pathogenesis: The route of infection of mucotaneous histoplasmosis is poorly understood. Two mechanisms may be possible: first, the portal of entry is the respiratory or gastro-intestinal tract and the mucocutaneous lesions occur secondary to the primary site; and the second possibility is that the skin and mucous membrane may be the primary sites of infection. In Cases 2 and 3, the second route of infection probably applied.

Remissions and exacerbations are seen, even without treatment (Bennet, 1967).

Methods of diagnosis

1. *Blood Smear* examination is the simplest and most available diagnostic procedure that can be used in the generalized type.

2. *Culture* from biopsy maternal obtained from ulcerated areas, blood or sputum, is a very reliable procedure. The mycelial form develops on nearly all the ordinary bacterial and fungus media kept at room temperature.

Bone marrow is desirable for culture in disseminated disease and is recommended in children (Rohn and Bond, 1953).

3. *Biopsy*—diagnosis by biopsy has been the most successful for all the methods (Lierle and Carr, 1951). In Parsons and Zarafonetis' (1945) series, 29 cases were successfully diagnosed by biopsy. The cases presented were diagnosed by the pathologist. The histology result is particularly important in localized histoplasmosis, because the clinical appearance does not usually suggest an infective disease. Histoplasma is demonstrated histologically by Hematoxilin and Eosin staining within the macrophages (Fig. 2). Toxoplasma may resemble histoplasma but is smaller and is usually not seen in macrophages. Blastomyces may be difficult to distinguish from histoplasma, but in well fixed tissue, blastomyces is multinucleate and histoplasma is uninucleate. Histoplasma is well stained by Gomori's Methenamine Silver (GMS) which eliminates many calcific artifacts that may be mistaken in other stains (Fig. 3) and by Giemsa (Fig. 4).

5. *Cutaneous Test.* The intradermal injection of a filtrate obtained from the liquid medium in which the fungus has grown, results in the production of erythema and a weal at the site of the injection. In known generalized histoplasmosis, about 50 per cent of patients show cutaneous anergy to histoplasma, while in chronic localized pulmonary disease, over 80 per cent of patients have positive cutaneous reactions (Rubin *et al.*, 1959).

A positive test indicates a previous or a recent infection and is only useful if the patient has been shown to have been negative previously.

6. *Complement Fixation Test* is a valuable procedure. A titre of 1:16 is suggestive of an infection with histoplasma, and fluctuations in titres indicates improvement or deterioration of the disease. An infected patient may, however, show a negative complement fixation text and a false positive reaction may be found in blastomycosis and coccidioidomycosis.

Treatment: Curtis and Grekin (1947) reviewed the use of antimony in the therapy of histoplasmosis with a doubtful result. In one of their cases, they used sulfadiazine, after which the patient still had microscopic evidence of histoplasmosis. They mentioned the use of irradiation in two cases reviewed from the literature with temporary palliation. Moore and Jorstad (1943) treated their cases with wide excision with unsuccessful results. A great variety of therapeutic agents have been tried, these include: Pentnucleotide, Fuadin, Neostam, Sodium Thiosulfate, Iodides, Ionized Metals, Potassium Tartrate,

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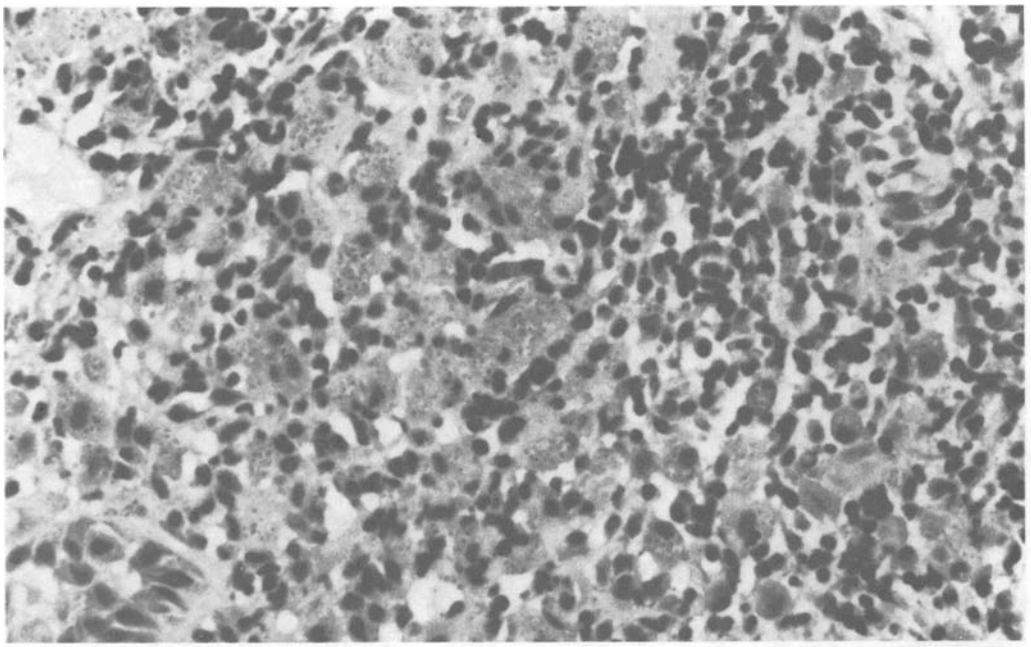


FIG. 2
H & E stained section, demonstrating histoplasma within the macrophages.

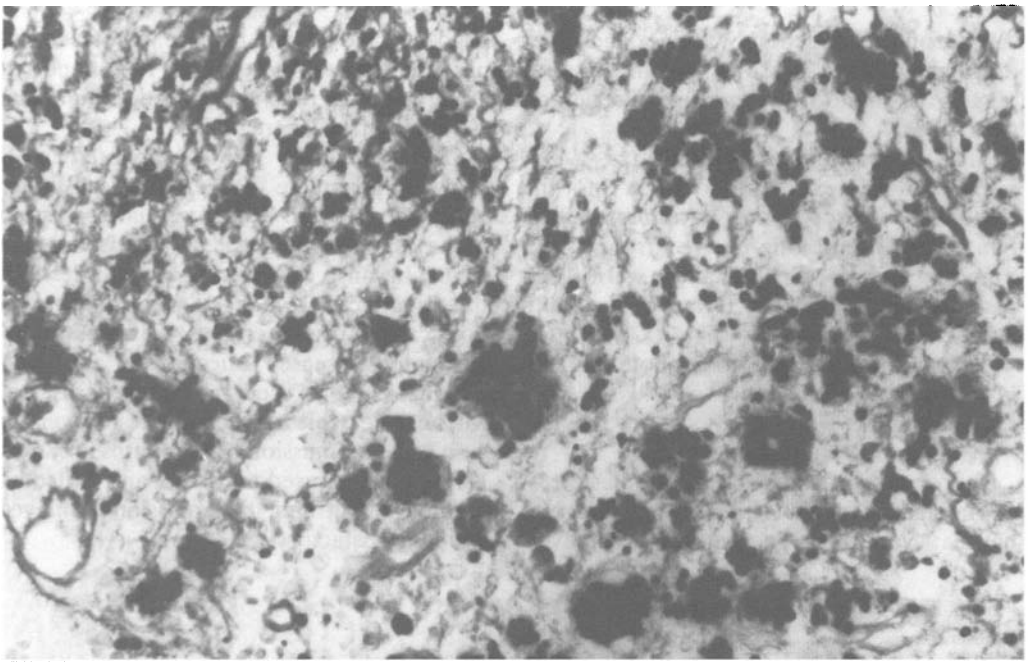


FIG. 3
Histoplasma is well stained with Gomori's Methenamine Silver (GMS), which eliminates many artifacts.

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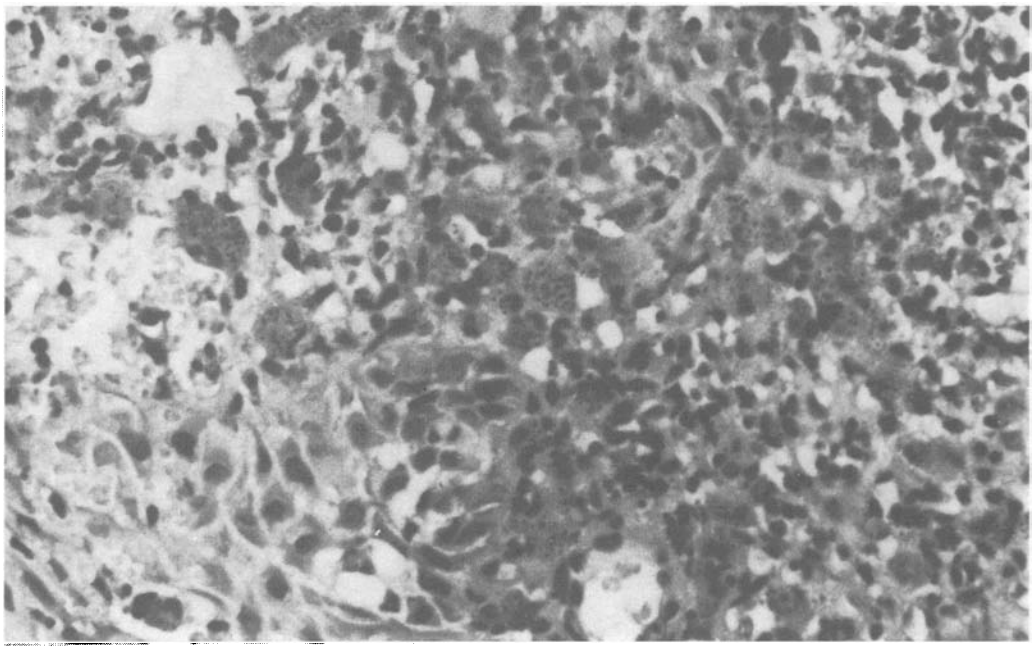


FIG. 4
GIEMSA staining of histoplasma.

Acetarsone, Autogenous Vaccines and other drugs showed the lack of a specific cure but none were found to be curative (Lierle and Carr, 1951).

In 1955, Gold (cited by Schwartz, 1981), introduced the use of Amphotericin B for the treatment of histoplasmosis. Amphotericin B is a polyene antibiotic derived from Streptomyces Nodosus, which occurs in soil in Tembladora on the River Orinoco in South America.

The main indications for Amphotericin B in histoplasmosis are:

1. Meningitis
2. Cavitating pulmonary disease
3. Progressive disseminated histoplasmosis.

The signs of toxicity of Amphotericin B are: nausea, vomiting, anorexia, chills, fever, headache and general malaise, reported in 80 per cent of cases. Butler *et al.* (1964) reported abnormal renal function in 85 per cent, as late as four years after treatment.

Our experience with Amphotericin B showed a complete recovery in case 3, after Ketokonazole had caused partial regression of the lesion. Amphotericin B was used in case 2 but, because of bone marrow depression, the treatment was changed to Miconazole. In both cases, Amphotericin B was used in disseminated disease. Miconazole and Ketokonazole were used in localized disease. Miconazole achieved a complete recovery in case 1 and a remission of 18 months in case 2. Ketokonazole, used in cases 2 and 3, had no curative effect and the remissions achieved were unsatisfactory.

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