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African histoplasmosis: a review

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Summary

African histoplasmosis caused by *Histoplasma capsulatum* var. *duboisii* is an important deep mycosis endemic in Central and West Africa and in the island of Madagascar. The disease is characterized by presence of granulomatous lesions in the skin, subcutaneous tissues and bones. Lungs and other internal organs are rarely involved. The natural reservoir of the etiological agent has only been recently discovered in a bat cave in Nigeria. The status of asymptomatic infection is not certain. Investigations on skin and serum reactivity have suggested frequent prevalence of asymptomatic infections due to *H. capsulatum* var. *duboisii* among the residents in the vicinity of the cave microfocus of the fungus. The exact portal of entry into the body is not known, but inhalation into the lungs and direct inoculation in the skin have been incriminated. Laboratory diagnosis is confirmed by *in vitro* conversion into large yeast forms (8-15 μ m in diameter) and by the demonstration of these forms within giant cells of tissues of experimentally infected animals. There are no major clean-cut physiological differences between the two varieties, viz. *capsulatum* and *duboisii*. The cell wall of *H. capsulatum* var. *duboisii* contains a glucan with β 1-4 linkages in addition to a galactomannan shared with *H. capsulatum* var. *capsulatum*. Like the var. *capsulatum* var. *duboisii* has marked proteinase and collagenase activities in both mycelial and yeast forms, suggesting a possible pathogenic role for these enzymes. Both varieties have a common exoantigen. The yeast form of *H. capsulatum* var. *duboisii* contains the antigen found in the serotype 1,4 of var. *capsulatum*. A monoclonal antibody test has been developed that can recognize some epitopes in *H. capsulatum* var. *capsulatum* but not in the var. *duboisii*. There is need to develop specific serological diagnosis for the disease. Also there should be greater international awareness about African histoplasmosis. Amphotericin B and several antimycotic azoles like ketoconazole, itraconazole and fluconazole have been successfully employed for treatment.

Key words

African Histoplasmosis, *Histoplasma capsulatum* var. *duboisii*, Natural infections in animals, Epidemiology, Diagnosis, Chemotherapy

Histoplasmosis africana: revisión

Resumen

La histoplasmosis africana causada por *Histoplasma capsulatum* var. *duboisii* es una importante micosis profunda endémica en el centro y el oeste de Africa y en la isla de Madagascar. La enfermedad se caracteriza por la presencia de lesiones granulomatosas en piel, tejidos subcutáneos y huesos. Raramente se ven afectados los pulmones y otros órganos internos. El reservorio natural del agente etiológico ha sido descrito recientemente en una cueva de murciélagos en Nigeria. Las investigaciones sobre la reactividad de la piel y el suero han sugerido una frecuente prevalencia de infecciones asintomáticas debida a *H. capsulatum* var. *duboisii* en los habitantes de los alrededores de la cueva. Se desconoce la vía exacta de entrada en el cuerpo, pero se ha apuntado que puede ser la inhalación y la inoculación directa en la piel. El diagnóstico de laboratorio se confirma por la conversión *in vitro* en grandes levaduras (8-15 μ m de diámetro) y por su demostración en el interior de células gigantes en los tejidos de animales infectados experimentalmente. No hay diferencias fisiológicas determinantes entre las dos variedades de *H. capsulatum*. La pared celular de *H. capsulatum* var. *duboisii* contiene glucano con enlaces β 1-4 además de galactomanano compartido por *H. capsulatum* var. *capsulatum*. Al igual que la variedad *capsulatum*, la variedad *duboisii* tiene importantes actividades proteínasa y collagenasa tanto en la forma micelial como levaduriforme, con un papel probable en la patogenia. Ambas variedades poseen un exoantígeno común. La fase levaduriforme de *H. capsulatum* var. *duboisii* contiene el antígeno encontrado en el serotipo 1,4 de la variedad *capsulatum*. Se ha desarrollado un test con un anticuerpo monoclonal que reconoce algunos epitopos en *H. capsulatum* var. *capsulatum* pero no en la variedad *duboisii*. Es necesario el desarrollo de un diagnóstico serológico específico para la enfermedad. También debería haber una mayor concienciación internacional sobre la importancia de la histoplasmosis africana. La anfotericina B, ketoconazol, itraconazol y fluconazol, se han empleado con éxito en el tratamiento de la histoplasmosis.

Palabras clave

Histoplasmosis africana, *Histoplasma capsulatum* var. *duboisii*, Infecciones naturales en animales, Epidemiología, Diagnóstico, Tratamiento

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African histoplasmosis (*histoplasmosis duboisii*) caused by *Histoplasma capsulatum* var. *duboisii* is an important deep mycosis, endemic in Central and West Africa between the latitudes 15°N and 10°S as well as in the island of Madagascar [1-3]. About 225 cases of the disease have been described, majority of them being reported from Nigeria, Niger, Senegal, Congo, Zaire and Uganda [4-9]. The other form of histoplasmosis, viz. histoplasmosis capsulati (classical histoplasmosis) caused by the variety capsulatum also occurs in Africa. Only the capsulatum form is so far known to occur in South Africa where it is very common. It also occurs sporadically in East Africa and rarely in Central and West Africa [2,9]. African histoplasmosis is characterized by presence of granulomatous and suppurative lesions in cutaneous, subcutaneous and osseous tissues [5-8,10]. The epidemiology of the disease is not properly understood. The information on the status of asymptomatic infections and the portal of entry of the fungus has been lacking [2]. This communication provides a concise update of the present state of knowledge of African histoplasmosis and its etiological agent.

CLINICAL FEATURES OF INFECTION IN HUMANS

African histoplasmosis involves usually the skin, subcutaneous tissues, lymph nodes and bones unlike classical histoplasmosis which generally involves lungs and mucosa and rarely shows cutaneous or bone lesions [2,4]. The cutaneous manifestations in African histoplasmosis are papular, nodular, ulcerative, eczematoid or psoriasisiform lesions [2,5-7]. The papules and nodules have a characteristic hyperpigmented halo around them, a pathognomonic sign of the disease. As papular and nodular lesions enlarge, the center ulcerates with or without an eschar. Subcutaneous lesions occur as suppurative abscesses or freely movable granulomata; they may arise from foci in the superficial flat bones or develop independently [10]. The abscesses present as firm, tender, hot swellings and later discharge pus containing yeast cells of the fungus. Patients with only skin or isolated bone lesions may have an indolent course and often improve spontaneously [4].

The predilection of *duboisii* histoplasmosis for the bone, particularly the elements of marrow is a characteristic of the disease. Thus bone involvement is very common, particularly in disseminated infections [10]. Osteolytic lesions tend to be multiple; skull, ribs, vertebrae, femur, humerus, tibia, and wrist are particularly involved [10]. Multiple skull lesions resemble the cranial defects in multiple myeloma or those seen in phalanges, and carpels in sarcoidosis. The granulation tissue from a vertebral or pedicle lesion may compress the spinal cord resulting in paraplegia [10]. The clinical and radiological features of a primary bone lesion may closely simulate neoplasm [10]. At first a symptomless cortical lesion is seen but it soon involves the periosteum, resulting in a tender painful swelling. It may later extend into the soft tissue with development of a cold abscess which usually ruptures with sinus formation. Extension to a contiguous joint may also occur resulting in osteoarthritis [11]. The lesions in organs other than bone may also mimic cancer. A few cases of skull involvement with neurological complications have also been reported [12]. Lymphadenopathy is usually confined to the area of local lesion but is generalized in the disseminated form of the disease. In the latter form of the disease, multiple cutaneous and bone lesions occur; miliary lesions are observed on the liver,

spleen and rarely in the lungs with systemic symptoms of fever, rigor and (if lungs are involved) productive cough and opacities in the hilar lymph nodes and lungs [13,14]. Mucosal involvement occurs in a few cases with small dome shaped papules on buccal or glossal mucosa [2].

Involvement of gastrointestinal tract is rare. However, Pichard *et al.* [15] estimated that 26% of all reported cases of histoplasmosis *duboisii* in Mali involved gastrointestinal tract. Several cases of large bowel involvement have been reported from Nigeria; the symptoms in these cases included abdominal pain, jaundice and diarrhea, the lesion in one case simulating carcinoma [16,17]. Adekunle *et al.* [18] reported a case of jejunal strictures with tubercles scattered over the surface of the bowel and adjacent mesentery. There is also a report of one patient dying of perforation of an ileocaecal granuloma [5]. Six cases of ocular involvement comprising one each manifesting as acute infection of lachrymal gland, and a cystic swelling resembling a dermoid cyst, and four of orbital granuloma have also been reported [19,20,21].

CLINICAL FEATURES OF INFECTION IN ANIMALS

Natural infections have been reported in baboon (*Cynocephalus babuin*, *Papio cynocephalus papio*). All infected baboons were detected in France and USA and they had originated from countries in West Africa [22]. The lesions occurred as small papules or ulcerative granulomas on the skin, subcutaneous tissue and lymph nodes. Osteolytic lesions were seen in the skull, metatarsals, metacarpals, phalanges, and coccygeal vertebrae. Infection due to *H. capsulatum* var. *duboisii* has not been recognized in cats, dogs and rodents which are known to be frequently infected with *capsulatum* variety [4].

NATURAL RESERVOIR OF HISTOPLASMA CAPSULATUM VAR. DUBOISII

A few reports of *duboisii* infections of humans associated with chicken runs and bat infested caves have suggested that the var. *duboisii* shares the same ecological niche as the var. *capsulatum* [4]. Al-Doory and Kalter in 1967 [23] reported isolation of *H. capsulatum* var. *duboisii* from pooled soil samples collected in Kenya but it was a misidentification as the isolate was later identified to be *H. capsulatum* var. *capsulatum* [1]. Recently, Gugnani *et al.* [24] discovered a natural reservoir of this fungus in soil admixed with bat guano in a bat cave in a rural area, viz. Ogbunike in Eastern Nigeria. The fungus was also recovered from the intestinal contents of one of the bats (*Nycteris hispida* -hairy tailed slit face bat with long ears) among the 35 bats of two species, viz. *N. hispida* and *Tadarida pumila* examined from the cave.

Identification of the isolates as *Histoplasma* was confirmed by exoantigen tests and by mating with tester strains of *H. capsulatum*. *In vitro* conversion to large yeast form on brain heart infusion agar and demonstration of large yeast cells (8-15 µm in diameter) within giant cells of tissues of experimentally infected mice confirmed their identity as *H. capsulatum* var. *duboisii*. Five of the isolates tested by mating were found to be (-) type. The (-) type was also found to be predominant among the 21 clinical isolates of *H. capsulatum* var. *duboisii* studied by Kwon-Chung [25]. *In vitro* interaction studies have indicated that *H. capsulatum* var. *duboisii* can coexist with other fungi like *Aspergillus fumigatus*, *Microsporium gypseum*, *Pseudallescheria boydii*, *Malbranchea gypsea* and *Chrysosporium* spp in an ecological niche [26].

EPIDEMIOLOGY

African histoplasmosis (*histoplasmosis duboisii*) is endemic in the African continent, essentially between the Tropics of Cancer and Capricorn [1,2] as well as in the island of Madagascar [3]. The disease has been detected in about 20 countries in tropical Africa located between 20°North and 20°South of Equator and extending from Senegal in the West to Tanzania in the East [2,4,5,7]. This is a region with high average rainfall, high humidity, and little variation in diurnal temperature and is almost identical to the endemic zone of African trypanosomiasis [2]. The two major African deserts, the Sahara and the Kalahari, are located North and South of the endemic region respectively. About 225 cases of the disease have been recorded; nearly 50% of them have occurred in Nigeria and 25% of them have been recorded in Niger, Senegal, Congo, Zaire and Uganda [5,7-9]. Although cases of African histoplasmosis have been diagnosed in USA and some countries in Europe and South America, these patients had been resident in areas in Africa endemic for the disease [4]. A case of African histoplasmosis described as an autochthonous case from Japan [27] was, in fact, typical of chronic classical pulmonary histoplasmosis due to an unusual isolate of *H. capsulatum* var. *capsulatum* [4]. A review of the cases shows a male:female ratio of the patients as approximately as 2:1; the age of the cases varied from 2 to 70 years, with the maximum number of cases occurring in the second decade [2,4-9]. The disease is not confined to any occupational group though agricultural workers, carpenters, and others engaged in outdoor activities have been more commonly affected. Some cases of human infection have been associated with chicken runs and bat associated caves.

The status of asymptomatic infections is regarded uncertain. Several skin testing surveys using the histoplasmin prepared from *H. capsulatum* var. *capsulatum* have been carried out in many parts of Africa [28-32]. These showed high rates of skin sensitivity in some areas, not corresponding with low frequency of occurrence of histoplasmosis *duboisii*. In another study [33], histoplasmins prepared from both *capsulatum* and *duboisii* varieties were simultaneously tested on 1313 subjects. An approximately 3% prevalence of skin positivity was recorded. Majority of the individuals who gave a positive reaction to *duboisii* antigen also reacted to the *capsulatum* antigen, thus indicating antigenic similarity. In an investigation of skin and serum reactivity among humans to histoplasmin in the vicinity of the natural focus (bat cave) of *H. capsulatum* var. *duboisii*, Muotoe-Okafor *et al.* [34] found a much higher prevalence (35%) of skin sensitivity among the cave guides, traders and farmers. Also 17 (9.4%) of 181 young adults, including farmers, palm oil workers resident in the vicinity of cave demonstrated precipitating antibodies to histoplasmin in their sera; three of the persons who were frequent visitors to the cave had both 'h' and 'm' precipitation bands. The results suggest that asymptomatic infections due to *H. capsulatum* var. *duboisii* may be quite common amongst the residents in the vicinity of the microfoc (bat cave) of the fungus, and some cases of active histoplasmosis *duboisii* may have, in fact, occurred but were missed due to lack of awareness among the physicians in the area.

There is very little information on association of AIDS with African histoplasmosis. Four such cases have been recorded in heterosexual Belgians who were long time residents in Africa [35-37]. Three cases of AIDS associated African histoplasmosis have also been described in indigenous Africans: one each in Zaire, Guinea

Bissau, and in Congo [37-39]. All the AIDS associated cases were disseminated rather than localized.

The portal of entry of the etiological agent has been a subject of speculation and has not been established. It has been suggested that the fungus may be inhaled and then haematogenously transferred to a favorable site, viz. skin, subcutaneous tissue, bone, lymph node for proliferation [2,5]. Transcutaneous route after trauma has also been suggested. The possible role of insect bites has been speculated [7,40].

LABORATORY DIAGNOSIS

The definitive diagnosis of African histoplasmosis is made by direct mycological examination, culture and histopathological examination. Serological tests are of little value [2]. The yeast form of *H. capsulatum* var. *duboisii* can be easily demonstrated in pus from skin lesions, abscesses, draining sinuses and bone lesions or biopsy material, as the organisms are usually numerous in the infected tissue. Yeast cells are thick walled and much larger (8-15 µm in diameter) as compared with those of var. *capsulatum*. The yeast cells may have fat droplets within them. They resemble the yeast cells of *Blastomyces dermatitidis* but can be distinguished by the fact that they are uninucleate and bud from a relatively narrow base whereas those of *B. dermatitidis* are multinucleate and bud from a broad base [4].

The fungus can be recovered in culture by inoculating clinical material on any of the several laboratory media, viz. Sabouraud dextrose agar, brain heart infusion agar or brain heart infusion blood agar supplemented with penicillin (20 units/ml) and streptomycin (40 units/ml) [2,4]. Colonial and microscopic morphology at room temperature (25°C-30°C) is identical to that of typical strains of *H. capsulatum* var. *capsulatum*. Microscopic examination shows microconidia and tuberculate macroconidia as seen in *capsulatum* variety. The organism can be easily converted to yeast form by inoculating on blood or brain heart infusion agar supplemented with cysteine or glutamine [2,24]. Initially small yeast forms are seen; later large yeast forms (8-15 µm in diameter) are formed and small *capsulatum* type yeast cells are not seen. Once a strain of *duboisii* variety has converted to large yeast form, the daughter cells are always of the large form. For definite confirmation of *H. capsulatum* var. *duboisii*, intratesticular injection of the organisms into mice or hamsters is a very useful procedure [4]. In the early course of orchitis, the yeast cells are mostly small and indistinguishable from those of var. *capsulatum*. The large cells gradually replace the small cells and by the end of 4-6 weeks, numerous large yeast cells typical of *duboisii* variety are found in the tissue, small yeast cells being absent. A commercially available nucleic acid hybridization test kit developed by Gen-probe (San Diego, USA) and chemoluminescent DNA probe developed by Padhye *et al.* [41] can identify an isolate as *H. capsulatum* much more rapidly than the exoantigen test but like the latter these can not distinguish *H. capsulatum* var. *duboisii* from *H. capsulatum* var. *capsulatum*.

HISTOPATHOLOGY

The histopathological picture is very characteristic and is distinct from that of classical histoplasmosis [5]. A typical lesion comprises largely of aggregates of multinucleate giant cells (Langhan type) containing numerous oval, doubly contoured, thick walled yeast cells that are larger (8-15 µm in diameter) and thicker walled than those

of *H. capsulatum* var. *capsulatum*. The yeast cells may sometimes occur in chains of four or five cells. Other types of inflammatory cells may be present, especially lymphocytes. In ulcerated skin lesions, an acute inflammatory response mixed with granulomatous reaction is observed. The organisms may be scanty in healing fibrotic lesions. Well organized granulomas with caseous centers and surrounding palisades of epithelial cells characteristic of classical pulmonary histoplasmosis are not seen. The histological picture in naturally infected animals (baboons) is similar to that in human lesions, with presence of granulomatous reaction with multinucleate giant cells containing large yeast forms of the organism [22]. The fungus is visible in H & E stained sections but is better demonstrated by silver methenamine, Gridley, or periodic acid Schiff stain.

PHYSIOLOGICAL CHARACTERS OF HISTOPLASMA CAPSULATUM VAR. DUBOISII

H. capsulatum var. *duboisii* is known to be urease negative unlike *H. capsulatum* var. *capsulatum* which is positive [42]. Conflicting results have been obtained by different investigators with regard to some other physiological tests, viz. hydrolysis of gelatin and tyrosine as mentioned by Domer and Moser [43]. To date, there are no distinct physiological differences between the two varieties. In a study of the biochemistry of the cell wall, Azuma *et al.* [44] showed *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii* to have an identical galactomannan as a common cell wall constituent, but the mycelial wall of *H. capsulatum* var. *duboisii* unlike that of *H. capsulatum* var. *capsulatum* contained a glucan with β 1-4 linkages in addition to β 1-3 linkages found in other dimorphic fungi. Vincent *et al.* [45] showed that var. *duboisii* had mitochondrial DNA restriction pattern identical to those of the majority of the strains of var. *capsulatum*.

Proteolytic enzymes have been considered important virulence factors in the pathogenesis of infections caused by dimorphic fungi [46, 47]. Very little work has been done on the proteinases and other enzymes of *H. capsulatum* var. *duboisii*. Moutoe-Okafor *et al.* [48] demonstrated the presence of an aspartyl proteinase in *H. capsulatum* var. *duboisii*. The activity was much more pronounced with the parasitic yeast form than with the mycelial form, suggesting an important role of the enzyme in the pathogenesis of infection. Possibly it breaks down the proteinaceous components of host tissue leading to typical necrosis observed in the lesions caused by the fungus [2]. Okeke and Muller [49,50] have reported collagenolytic and elastinolytic proteinases in the yeast form of this fungus and have suggested that these enzymes may function as virulent markers for the fungus.

IMMUNOLOGY

Inherent immunity or immunity resulting from recovery from subclinical or clinical infections has not been established in African histoplasmosis. There are some immunological differences between *H. capsulatum* var. *duboisii* and *H. capsulatum* var. *capsulatum*. Pine *et al.* [51] were able to prepare fluorescent antisera which could distinguish between the two varieties. However, Kaufman and Blumer [52] reported that the yeast cells of *H. capsulatum* var. *duboisii* (and also of *B. dermatitidis*) contained the antigens demonstrated by *H. capsulatum* var. *capsulatum* serotype 1, 4 and the two varieties were indistinguishable in standard serological assays. Fadulu and Larsh

[53] found that *capsulatum* and *duboisii* varieties had one antigen in common but m antigens of the two varieties were different. Later Hamilton *et al.* [54] prepared monoclonal antibodies (MAB) that could be used in identifying certain epitopes in *capsulatum* variety but not in the *duboisii* variety. This suggests that MAB may be of considerable value in diagnosis of histoplasmosis where both classical and African forms of the disease occur.

CHEMOTHERAPY

The isolated lesions of African histoplasmosis are amenable to surgical removal and may also heal spontaneously. Patients with multiple lesions or disseminated infections require chemotherapy. Amphotericin B has been the traditional drug of choice and has been used successfully in many disseminated cases [2,5,8], given as slow intravenous infusion in glucose for several weeks. A total dose of 1-3 g is required for a full course of treatment. Egere *et al.* in 1978 [54] reported successful treatment of one case with cotrimoxazole. Later Ajayi *et al.* in 1986 [21] reported dramatic success with this drug in the therapy of four cases of orbital histoplasmosis *duboisii*; one of these case had been treated unsuccessfully with amphotericin B. Among several azole antimycotics tried for treatment of African histoplasmosis, ketoconazole and itraconazole show good promise as their efficacy has been demonstrated for a large number of cases of the disease [8,56,57]. Recently Gugnani *et al.* [58] successfully treated a case of African histoplasmosis with fluconazole.

CONCLUSION

African histoplasmosis is a clinical entity distinct in clinical features and histopathology from classical histoplasmosis. The disease has a wide clinical spectrum, presenting varying features. The recent discovery of natural focus of the etiological agent, *H. capsulatum* var. *duboisii* in a bat cave should stimulate search for microfoci in other parts of West Africa. Detection of several cases of subclinical infection among the residents around the cave emphasizes the need for intensive epidemiological investigations on African histoplasmosis. The exact portal of entry of the fungus in the human host has yet to be established. There is also need for intensive research on the immunology of the disease. It is hoped that recent advances in immunological techniques and molecular biology will help in the development of specific serological diagnosis of the disease. At present only a few case of this disease associated with AIDS have been known. As AIDS is currently spreading to rural areas of Africa, the need for surveillance of AIDS associated infections due to *H. capsulatum* var. *duboisii* and other systemic fungal pathogens is obvious. With increased travel between Africa, and Europe and the American Continent, there is also need for greater international awareness about the clinico-pathological spectrum of African histoplasmosis.

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