

African Histoplasmosis*

by

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KEYWORDS. — Africa ; African Histoplasmosis ; AIDS ; Classic Histoplasmosis ; *Histoplasma capsulatum* ; *Histoplasma duboisii* ; Histoplasmosis ; Mycoses.

SUMMARY. — African histoplasmosis, which is only observed in patients living in or having lived in Africa, and American histoplasmosis, which can also be acquired outside North America, including Africa, are distinct clinical entities. However, the causal *Histoplasma* species (or varieties) are still only definitely separated on their *in vivo* morphology. Infections due to *H. capsulatum* are acquired by the respiratory route, whereas a digestive route in African histoplasmosis may be re-considered. *H. capsulatum* AIDS-associated infections are frequently reported, mainly in the North American endemic areas. In contrast AIDS-associated African histoplasmosis cases are rather uncommon. Several natural habitats of *H. capsulatum*, i.e. places where infective saprobic propagules are produced, have been repeatedly discovered in endemic and non-endemic areas (e.g. Shaba in Zaire). So far a natural focus of *H. duboisii* has only once been discovered, quite recently in Nigeria.

TREFWOORDEN. — Afrika ; Afrikaanse histoplasmose ; AIDS ; Klassieke histoplasmose ; *Histoplasma capsulatum* ; *Histoplasma duboisii* ; Histoplasmose ; Mycosen.

SAMENVATTING. — *Afrikaanse histoplasmose.* — Afrikaanse histoplasmose, die alleen bij patiënten die in Afrika leven of hebben verbleven voorkomt, en Amerikaanse (of klassieke) histoplasmose, die men ook buiten Noord-Amerika, onder meer in Afrika kan opdoen, zijn twee klinische entiteiten. De *Histoplasma*-soorten (of variëteiten) die deze aandoeningen veroorzaken, kunnen tot op heden nog steeds alleen op basis van hun *in vivo* morfologie onderscheiden worden. Infecties door *H. capsulatum* ontstaan via de respiratoire route. Wat betreft Afrikaanse histoplasmose is de mogelijkheid van een ingangsweg via het darmkanaal weer ter sprake gekomen. AIDS-geassocieerde *H. capsulatum*-infecties zijn zeer frequent, voornamelijk in de endemische gebieden van de V.S. Integendeel, tot op heden werden maar heel weinig gevallen van Afrikaanse histoplasmose bij AIDS-patiënten waargenomen. Meerdere vindplaatsen waar *H. capsulatum* als saprofit leeft en infectieve sporen produceert zijn reeds lang gekend, niet alleen in de endemische streken maar ook elders, onder meer in Shaba, Zaire. Een natuurlijke vindplaats van *H. duboisii* werd pas recent voor het eerst ontdekt in Nigeria.

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MOTS-CLES. — Afrique ; Histoplasmose africaine ; SIDA ; Histoplasmose classique ; *Histoplasma capsulatum* ; *Histoplasmose duboisii* ; Histoplasmose, Mycoses.

RESUME. — *L'histoplasmose africaine*. — L'histoplasmose africaine, qui n'est observée que chez des patients vivant en Afrique ou ayant séjourné en Afrique, et l'histoplasmose américaine ou classique qui existe également en dehors de l'Amérique du Nord, et notamment en Afrique, constituent deux entités cliniques. Les espèces ou variétés d'*Histoplasma* qui les causent ne peuvent être identifiées que sur base de leur morphologie *in vivo*. Les poumons constituent la porte d'entrée des infections à *H. capsulatum*, alors que pour l'histoplasmose africaine on évoque la possibilité d'une pénétration digestive. L'histoplasmose classique est fréquente chez les patients atteints du SIDA, principalement dans les régions endémiques des États-Unis. Par contre, jusqu'à présent très peu de cas d'histoplasmose africaine ont été signalés chez ces patients. On connaît plusieurs endroits où *H. capsulatum* vit à l'état saprophytique, produisant ses spores infectantes. Par contre, ce n'est que récemment que pour la première fois *H. duboisii* a été isolé de l'environnement, au Nigéria.

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Histoplasmoses are deep mycoses, acquired from the environment and caused in man by at least two species (or varieties) of fungi belonging to the genus *Histoplasma* : *H. capsulatum* Darling 1906 (or *H. capsulatum* var. *capsulatum*), and *H. duboisii* (VANBREUSEGHEM 1952) (or *H. duboisii* var. *duboisii*). Since sexual reproduction may be obtained by crossing complementary mating types of *H. duboisii* and *H. capsulatum* strains, the status of varieties is preferred by most authors.

The former is the etiologic agent of classic histoplasmosis (sometimes also called "American histoplasmosis"). This form as well as the forms *histoplasmosis capsulati* and *histoplasmosis duboisii* have been rejected by an ISHAM sub-committee on "nomenclature of Mycoses" in 1991, Convenor : F. C. Odds (ODDS *et al.* 1992), which is mainly endemic in the Mississippi and the Ohio river valleys, but has also been reported to occur in more than fifty countries outside the USA, including fifteen countries in Africa (Table 1).

H. duboisii is the agent of African histoplasmosis and only occurs in Africa (between 15° N and 10° S). The twenty-nine countries from where cases have been reported are listed in table 1. It is noteworthy that in Zaire the majority of cases have been reported from the Kasai province (RENOIRTE *et al.* 1967).

J. T. DUNCAN (1946) in his paper entitled "A unique form of *Histoplasma*" was probably the first to notice that there could exist another form of histoplasmosis in Africa. However, A. DUBOIS, P. G. JANSSENS & P. BRUTSAERT (1952) were the first to describe this disease as a clearly distinct entity and Vanbreuseghem was the first to describe its agent as a new species, dedicated to professor Albert Dubois.

R. Vanbreuseghem has devoted not less than 33 of his 331 papers to his *Histoplasma* : the topic "African histoplasmosis" is certainly not out of place

Table 1
Distribution of histoplasmosis case reports in Africa

COUNTRY	CLASSIC	AFRICAN
Angola		x
Benin	x	x
Burkina Faso		x
Cameroon	x	x
Central African Rep.		x
Chad		x
Congo	x	x
Djibouti	x	
Ethiopia		x *
Gabon	x	x
Gambia		x
Ghana		x
Guinea		x
Guinea-Bissau		x
Ivory Coast	x	x
Kenya	x	x
Liberia		x
Madagascar		x
Malawi		x
Mali		x
Niger		x
Nigeria	x	x
Rwanda	x	x
Senegal		x
Sierra Leone		x
Somalia	x	
South Africa	x	
Sudan	x	x **
Tanzania		x
Togo		x
Uganda	x	x
Zaire	x	x
Zimbabwe	x	

* ADERAYE & SEIFU 1987

** GUMAA *et al.* 1988

(adapted from SURMONT & VANDEPITTE 1991)

in this “Fourth Raymond Vanbreuseghem Conference on Human Mycoses in Tropical Countries”.

It has become a tradition to speak about African histoplasmosis and its agent making comparisons with classic histoplasmosis and with *H. capsulatum*, its elder brother.

Following items are discussed : morphological features, portal of entry, clinical manifestations and treatment, AIDS-associated histoplasmoses and natural habitat of the agents.

1. Morphology

In culture, i.e. in their saprobic state, *H. duboisii* and *H. capsulatum* are alike producing the same kind of asexual spores (large, diagnostic macroconidia, with a thick wall covered with digitate protuberances and small [2-4 μm] microconidia). When grown at 37 °C on a suitable medium, these dimorphic fungi may be converted to a yeast form, which is however also similar in both species.

The only way to distinguish the two species (or varieties) on a morphological basis is their relative sizes in host tissue, i.e. *in vivo*. The diagnostic ovoid yeast cells of *H. duboisii in vivo* are large, measuring 8 to 15 μm , whereas the parasitic form of *H. capsulatum* is represented by small (2-3 μm) yeast cells. Hence the use of the terms “large form” histoplasmosis versus “small form” histoplasmosis or even *histoplasmoses à formes duboisii* versus *histoplasmoses à formes capsulatum*. However, a pitfall remains : as was shown by VANBREUSEGHEM (1952) in his first studies on *H. duboisii*, at the early stage of experimental infections (e.g. in guinea-pigs, hamsters), the tissue form of *H. duboisii* is similar to that of *H. capsulatum*, i.e. small yeast cells (2-3 μm). Subsequently, the typical large *duboisii* cells gradually appear.

The same happens in human infections hence the title of a publication by DEVRESE *et al.* 1961 : “Histoplasmoses à formes ‘capsulatum’ causée par *H. duboisii* Vanbreuseghem 1952”. (Histoplasmosis with “capsulatum” forms caused by *H. duboisii* Vanbreuseghem 1952.) Therefore, several cases of histoplasmosis observed or acquired in Africa and diagnosed solely by histology are erroneously attributed to *H. capsulatum*. This is true for rapidly evolving cases, particularly for those reported in AIDS patients.

2. Portal of entry

It is widely accepted that infections due to *H. capsulatum* are acquired by the respiratory route after the inhalation of airborne spores originating from saprobic niches (pulmonary initial manifestations ; possibility of residual pulmonary calcifications).

The portal of entry in African histoplasmosis remains questionable : primary pulmonary infection is not recognized and the possibility of an entry via the digestive tract, already suggested by Vanbreuseghem in DEVREESE *et al.* (1961), has recently re-emerged (PAKASA & NSIANGANA 1991, MARJOLET 1992). Several reports of unifocal intestinal localizations might add to the observations of these last authors.

3. Clinical manifestations and treatment

Primary classic histoplasmosis is, depending on the immunological status of the patient and/or the number of inhaled infective propagules, usually a self-limiting disease.

In its secondary form it may evolve to a progressive lung disease or a disseminated disease involving the cells of the reticulo-endothelial system. Both acute and chronic forms are seen. The mild chronic disease or adult type is also reported in our countries almost exclusively in males, years after their return from tropical regions, in Belgium mainly from Zaire.

The hallmark of this condition as stated by GOODWIN & DES PREZ (1978) is the development of an oropharyngeal ulcer often suggesting malignancy and leading to a biopsy from which the correct diagnosis is made.

As already mentioned, the primary form of African histoplasmosis is apparently unrecognized. The secondary form is mainly characterized by skin, lymph node and bone involvement. The cutaneous lesions are polymorphic, presenting as papules, nodules, ulcerations and proliferative processes. In about one third of the cases, osteolytic lesions are seen. Dissemination to various deep organs may occur sooner or later.

The clinical presentation of both diseases in AIDS patients is, as occurs with other opportunistic infections in this group of patients, often divergent from the usual pattern.

As in other deep mycoses, the choice of amphotericin B (intravenous) versus orally active azoles such as itraconazole depends on the severity of the disease or the immunological status of the patient. Relapses seem to occur more frequently in *H. duboisii* infections.

4. AIDS-associated histoplasmoses

AIDS-associated *H. capsulatum* infections have repeatedly been reported in various countries, especially of course in the endemic areas of North America, where its prevalence ranges from 5-28 %, being frequently the AIDS-defining illness in patients with low CD4 counts (KAUFFMAN 1994).

In contrast, AIDS-associated African histoplasmosis is apparently uncommon. This leads some authors to raise the question : "Is African histoplasmosis

an opportunistic fungal infection in AIDS?" (CARME *et al.* 1990). In the paper by GEFFRAY *et al.* (1994) reporting on four cases observed in Zairians, only seven other cases from the literature are cited (including two cases observed in Belgium by PEETERS *et al.* 1987 & ARENDT *et al.* 1991).

In an analysis of imported histoplasmosis cases observed in France during the twenty-five last years, DUPONT *et al.* (1996) make mention of twenty-two cases due to *H. duboisii* from which only one was observed in an HIV-infected patient.

Are the cases under-diagnosed in the endemic areas or are the infections only acquired in remoted rural areas? This argument is also used to explain the scarcity of AIDS-associated paracoccidioidomycosis in South America.

5. Natural habitat

A last difference between classical histoplasmosis and African histoplasmosis concerns the knowledge about the natural habitat of their two agents, i.e. the biotopes where they live as saprobic mould, producing infective propagules and where infections thus are presumed to occur.

It has been known for a long time that in the endemic regions of the USA, soil enriched with guano constitutes a suitable substrate for the growth of *H. capsulatum*. This includes chicken houses, startling roots and caves inhabited by bats (hence the name of cave disease). This last biotope has also been discovered in other countries including African countries (e.g. in Shaba as reported by BOVY *et al.* 1960).

Despite several surveys it was only recently, in 1991, that *H. duboisii* was for the first time isolated from a saprobic source, namely from a bat cave in Ogbunike, Anambra state in Nigeria (GUGNANI *et al.* 1994). It is interesting to note that it was only conceded that the identification of the species as *H. duboisii* was correct after the observation of large, *duboisii* yeast cells in experimental animal infection.

Conclusion

From this short overview on African histoplasmosis it can be concluded that further studies are still needed to clarify several aspects of this disease mainly in the field of its epidemiology and of the ecology of the causative fungus.

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