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Research Paper:
Cranial and Spinal Locations of *Histoplasma Capsulatum Var. Duboisii* in Brazzaville, Congo

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ABSTRACT

Background and Aim: Histoplasma capsulatum var. duboisii is a rare fungus that is endemic in the Sahara and Madagascar in southern Africa. The present study was conducted to explain the confirmed cases of histoplasmosis.

Methods and Materials/Patients: This retrospective study was conducted at the Division of Neurosurgery of Brazzaville teaching hospital in the Republic of Congo. The clinical records of all of the confirmed cases admitted between January 2014 and December 2017 were reviewed.

Results: All of the five cases of confirmed histoplasmosis, including two women and three men, with a mean age of 42 years old, admitted to the Division of Neurosurgery over four years were immunocompetent to HIV. Radiological imaging identified a localized form of cold abscess in two of the patients and disseminated forms in three male cases. Lung lesions were also observed in two patients with multilevel spondylodiscitis and lung diseases, and clavicular osteitis in the other patient. Clavicular osteitis was also found to be associated with cutaneous fistulization in one of the patients, with cutaneous nodules in the second patient and with cutaneous nodules and pulmonary lesions in the third. Appropriate outcomes were observed for the localized forms but undesirable ones for the disseminated forms. Four patients had received medical and surgical treatments. This treatment caused an appropriate evolution in patients with localized forms and an undesirable evolution in the two scattered forms. These patients died upon admission due to the complications associated with their severe neurological condition. The final case died before beginning the antifungal treatment following a septic shock with the fistulization of osteitis clavicularis as its potential cause.

Conclusion: Although infections with Histoplasma capsulatum var. duboisii are rare, the lack of comprehensive knowledge on this fungus in the majority of medical staff can explain the delays in treating these infections. Microbiological analyses are therefore required to be performed on pathological materials in the event of suppuration to assist with early diagnosis and effective management.

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Highlights

- Despite the rare infections with Histoplasma capsulatum var. duboisii, the lack of knowledge of this fungus in the majority of medical staff can explain delays in treating these infections.

- To the best of the authors' knowledge, no clinical trials have yet been conducted on the efficacy of treating histoplasmosis associated with Histoplasma capsulatum var. duboisii.

- Improving the prognosis requires the microbiological analyses of all the pathological materials obtained from the infectious lesions.

Plain Language Summary

Histoplasma capsulatum var. duboisii is a rare fungus, endemic in the Sahara and Madagascar. The present study was conducted at the Division of Neurosurgery, Brazzaville hospital in Congo to explain the confirmed cases of histoplasmosis. The clinical records of all of the confirmed cases admitted between January 2014 and December 2017 were reviewed. All of the five cases of confirmed histoplasmosis, including two women and three men, with a mean age of 42 years old, admitted to the Division of Neurosurgery over four years, were immunocompetent to HIV. Radiological imaging identified a localized form of cold abscess in two of the patients and disseminated forms in three male cases. Lung lesions were also observed in two patients with multilevel spondylodiscitis and lung diseases, and clavicular osteitis in the other patient. Clavicular osteitis was also found to be associated with cutaneous fistulization in one of the patients, with cutaneous nodules in the second patient and with cutaneous nodules and pulmonary lesions in the third. Four patients had received medical and surgical treatments. This treatment caused an appropriate evolution in patients with localized forms and an undesirable evolution in the two scattered forms. These patients died upon admission from the complications associated with their severe neurological condition. The final case died before beginning the antifungal treatment following a septic shock with the fistulization of osteitis clavicularis as its potential cause. Although infections with Histoplasma capsulatum var. duboisii are rare, the lack of comprehensive knowledge on this fungus in the majority of medical staff can explain the delays in treating these infections. Microbiological analyses are therefore required to be performed on pathological materials in the event of suppuration to assist with early diagnosis and effective management.

1. Introduction

As a rare fungal infection not included in opportunistic infections associated with AIDS [1-5], histoplasmosis caused by *Histoplasma capsulatum var. duboisii* is endemic in the south of the Sahara and Madagascar in Africa [1, 3, 6]. It remains reported as small series, perhaps explaining the limited knowledge of its epidemiology [1]. This fungus has only been isolated in the soil, and its original biotope is yet to be clarified [1, 7]. Although contamination with this fungus appears to be of aerial origin, transcutaneous pathways through telluric wounds and digestive pathways have been reported [1, 7]. Inhaled spores develop into a large yeast 8-15 µm in length, which proliferate in the cell, and turn into mononuclear phagocytes through phagocytosis by the macrophagic system.

Histoplasma capsulatum var. duboisii lymphatically spreads and may invade several organs [1]. Pulmonary involvement often goes unnoticed [1]. As the most frequent type of lesion, cutaneous lesions resemble the molluscum contagiosum and take the form of often-umbilicated papules or nodules on the limbs and face. Ulcers are often observed, especially in the folds [1].

The localized or disseminated lesions are found in several organs, including the skin, muscles, ganglions, joints, and bones. The skull and spine are still rarer sites, and often taken for other, more frequent infections such as tuberculosis [1]. The present study was conducted to explain clinical and morphological presentations and methods of treating infections with *Histoplasma capsulatum var. duboisii* in Brazzaville between January 2014 and December 2017.

2. Methods & Materials/Patients

The present retrospective study was conducted at the Division of Neurosurgery of Brazzaville teaching hospital in the Republic of Congo from January 2014 to December 2017. The variables comprised of gender, age, duration of the symptoms and site of the lesions. The para-clinical assessments consisted of morphological examinations, mainly including Computed Tomography (CT) and MRI, and blood tests, including Blood Count (BC), Sedimentation Rate (SR), C-Reactive Protein (CRP) and Retroviral Serology (RVS). The treatment alternatives were medical and surgical. Eight hundred mg of itraconazole was used daily in the antifungal therapy for 12 weeks, and necrosectomy was performed as the surgical procedure to flatten the scalp abscesses. Excising sequestra from the occipital bone was performed. The complete regression of the clinical and biological signs of infection was the criterion for recovery in these patients.

Descriptive statistics were used to describe the frequencies and percentages of the variables. All the patients confirmed with *Histoplasma capsulatum var. duboisii* were sampled during the study period.

Data collection and statistical analysis

The small sample used in the present study was a limitation that prevented drawing statistical comparisons.

3. Results

Histoplasmosis caused by *Histoplasma capsulatum var. duboisii* was confirmed in five of the patients aged 29-60 years old with a mean age of 42 years old, including two females and three males. The symptoms emerged in 2-8 months with a mean duration of 5 months (Table 1). Cranial lesions were observed in the two women with cold abscesses of the scalp and disseminated vertebro-medullary lesions in the three men. The clinical picture involved paraplegia caused by spinal cord compression, thoracic spinal anesthesia, and urinary and fecal incontinence. According to Figure 1, cutaneous nodules and pneumopathy were observed in both of the patients who were diagnosed with multifocal tuberculosis and treated accordingly before the right diagnosis was made. An abscess opposite the right clavicle was observed in the third patient. The paraclinical assessments included blood and morphological examinations.

The blood parameters examined in all of the patients included hyperleukocytosis, acceleration of the SR, elevation of CRP and negativity of RVS. The morphological examinations included cranial CT, which showed a subcutaneous hypodense collection in the two patients. This collection was associated with occipital osteitis only in one of these patients. The morphological assessments performed in patients with vertebro-medullary lesions included vertebro-medullary MRI and thoracic CT.

Vertebro-medullary MRI showed the second and third stages of ankylosing spondylitis with a paravertebral fluid collection and a compressive epiduritis in all the three patients (Figure 2). Thoracic CT also showed pulmonary lesions in the two patients and right clavicular osteitis in one patient. The advanced stage of spinal cord compressions reduced surgical needs for excising paravertebral and epidural abscesses in the two patients following a one-level laminectomy. A fistulized abscess next to the right clavicle was also observed in the last patient.

According to Figure 3, the mycological and histological examinations of the operative material and the pus in the cutaneous and periclavicular lesions suggested the presence of *Histoplasma capsulatum var. duboisii*. The antimycotic treatment was performed with 800 mg of itraconazole for 12 weeks at the cranial sites of two of the patients and the spinal site of the two others.

Healing was observed as the outcome in the patients with cranial lesions after three years. Two of the patients with spinal lesions in a multifocal context died following a septic shock originating from a periclavicular location and one before beginning the antimycotic treatment due to bedsore. The death of the latter case abruptly occurred at home, although the infectious picture was evolving satisfactorily.

4. Discussion

As a rare deep mycosis, histoplasmosis mainly affects adults although pediatric cases have been also reported [6, 8-10]. The present study reported five cases with histoplasmosis in 4 years and included 3 men and 2 women of 29-60 years of age. The mean age was 27.2 years in the case-series reported by Dare [11], which was mainly conducted on men. The mean age was 20.5 in a study by Pakassa [8] conducted mainly on females. Our study investigated three cases of generalized lesions and two localized lesions, whereas approximately 80% of literature has been devoted to the localized forms and 20% to the disseminated forms [2, 10].

Table 1. Summary of the clinical and para-clinical data of the patients

Patient No.	1	2	3	4	5
Age (year)	30	29	60	52	34
Gender	Female	Female	Male	Male	Male
Profession	Unemployed	Secretary	Administrator	Construction worker	Sawyer
Duration of the symptoms (month)	4	2	8	6	5
Lesions and localization	Scalp abscess: occipital-median	Scalp abscess: right parietal	Thoracic medullar compression, pneumonia, nodules of the skin	Thoracic medullary compression, nodules of the skin	Thoracic medullary compression, abscess of the right chest
Laboratory findings	WCC: 11200 ESR: 35/58 CRP: 18 HIV: Negative	WCC: 10700 ESR: 25/44 CRP:16 HIV: Negative	WCC: 16300 ESR: 70/105 CRP: 63 HIV: Negative	WCC: 17400 ESR: 50/93 CRP: 47 HIV: Negative	WCC: 13200 ESR: 85/123 CRP: 97 HIV: Negative
Morphological report	CT: occipital osteitis	CT: Normal	CT, MRI: Medullary compression T10-T11	CT, MRI: Medullary compression T4-T5	CT, MRI: Medullary compression T6-T7
Mycological report	*Histoplasma duboisii*	*Histoplasma duboisii*	*Histoplasma duboisii*	*Histoplasma duboisii*	*Histoplasma duboisii*
Histological report	*Histoplasma duboisii*	Not performed	*Histoplasma duboisii*	*Histoplasma duboisii*	Not performed
Treatment	Surgical, itraconazole	Surgical, itraconazole	Surgical, itraconazole	Surgical, itraconazole	Not performed
Progression	Favorable	Favorable	Death	Pressure sores, septic shocks, death	Septic shocks, death

Cranial lesions observed as the localized forms in all the women with scalp abscesses had been treated as abscesses with common germs using flattening and antibiotic therapy. No healing in these infectious lesions caused presentation to the study department. The disseminated forms included vertebro-medullary localizations observed in the men. As potentially-bulky abscesses or subcutaneous masses at the subcutaneous level, these lesions were observed in the thorax of one of the patients, while a cranial lesion was identified in two of the other cases. Cervical, axillary and inguinal adenopathies can be bulky and simulate tuberculous adenitis or cold abscesses. The bone lesions were of a lytic type found at cranial, maxillary, femoral, tibial and spinal levels where they simulated Pott's disease. Other potentially-affected viscera included the liver, the spleen, and adrenal glands.

The potential problems associated with histoplasmosis with *Histoplasma capsulatum var. duboisii* include the differential diagnosis of tuberculosis and leprosy [1]. This infection is required to be differentiated from molluscum contagiosum in case of isolated nodules on the skin, in general, and on the face, in particular [2]. The diagnosis was primarily mycological from pathological products such as pus, serosities, and affections of ganglia. This examination showed large forms of yeast 5-20 µm in length with a double contour wall in the shape of an 8 or a fresh lemon after staining with MGG. The filamentous forms can be shown on Sabouraud agar preferably not necessarily at 25° C or 37° C [1, 2].

Anatomopathological findings can result in more reliable diagnoses even in the absence of these lesions, as epithelioid and purulent granulomas, lymphocytes and neutrophils are present as well as numerous giant cells containing many large thick-wall yeasts 10-15 µm in diameter divided by budding [12]. Narrow real-time and semi-nested PCR appear helpful in diagnosing histoplasmosis in blood and tissue samples caused

Figure 1. Scattered form of skin lesions in histoplasmosis caused by *Histoplasma capsulatum var. duboisii*

Figure 2. Magnetic resonance images in T2 without a gadolinium injection into the sagittal section

It shows spondylitis with compressive epiduritis and soft tissue extension in T4-T5. Vertebral localization in the disseminated form of Histoplasmosis caused by *Histoplasma capsulatum var. duboisii*.

by *Histoplasma capsulatum var. duboisii* [8, 13, 14]. An extension to the *duboisii* variety can be useful for this underdiagnosed disease.

To the best of the authors' knowledge, no clinical trials have yet been conducted on the efficacy of treating histoplasmosis associated with *Histoplasma capsulatum var. duboisii*. The guidelines of the Infectious Diseases Society of America can be extrapolated to Histoplasma capsulatum var. capsulatum [7, 15]. The severe forms of the lesions can, therefore, be treated by intravenously administering 0.7-1 mg/kg of amphotericin B per day for 2-4 weeks along with 200-400 mg of itraconazole daily

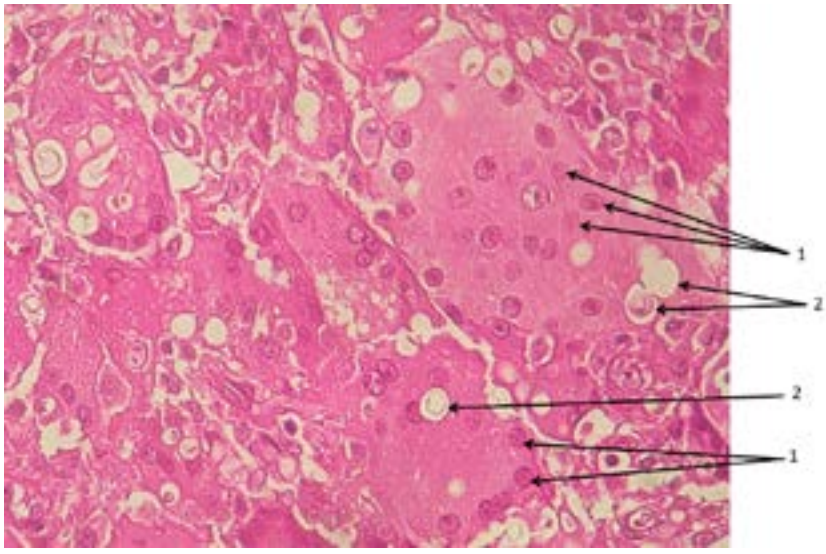

Figure 3. *Histoplasma capsulatum var. duboisii*

Several *nuclei in giant granuloma* cells containing "levuriform" elements with double contours and refractive spherical inclusions in their cytoplasm thick-wall oval; high magnification (G40X). HE coloring (Source: Prof. PEKO et al., Laboratory of Pathological Anatomy, University Hospital of Brazzaville).

for below 3 months [15]. Itraconazole can be prescribed for ten days from the onset of the less severe forms [2]. Compared to the formerly-used ketoconazole, significantly higher effectiveness of itraconazole [8] explains its immediate use in patients in the present study. The drainage and flattening of an abscess or removal of an easily-extirpable subcutaneous mass can reduce the parasitic load [1]. Clinical and biological monitoring is required for minimizing the risk of recurrence after completing the treatment [1, 7].

The evolution was more favorable for the localized forms than that for the disseminated ones. The present study reported mortality in all of the disseminated cases. Loulergue also reported mortality as 20% in the disseminated forms of HIV-positive subjects [7]. The diagnostic delay associated with the complete neurological charts can explain the deaths in the present series.

Study strengths and limitations

The present study provided the evidence required for making changes after identifying problems with diagnosing and managing infections with *Histoplasma capsulatum var. duboisii* in Brazzaville. The limitations of the present study were the retrospective type of data and the small sample size.

5. Conclusion

Despite the rare infections with *Histoplasma capsulatum var. duboisii*, which is endemic in the Sahara and Madagascar, the lack of knowledge about this fungus in the majority of medical staff can explain delays in treating these infections. Improving the prognosis requires the microbiological analyses of all the pathological materials obtained from the infectious lesions.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Authors contributions

Design and writing – original draft preparation: Leon Boukassa; Data collection: Olivier Brice Ngackosso and Sinclair Brice Kinata Bambino; Statistical aspects: Hugues Brieux Ekouele Mbaki; Conceptualization and supervision: Hugues Brieux Ekouele Mbaki, Sylvain Ngounda Monianga, Jean Felix Pecko andKhedel Mavoungou Biatsi.

Conflict of interest

The authors declared no conflict of interest.

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