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Fatal misdiagnosis of progressive disseminated histoplasmosis

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ABSTRACT

Disseminated histoplasmosis is the form of a mycosis caused by the fungus *Histoplasma capsulatum* that mainly occurs in immunosuppressed hosts, usually with non-specific symptoms. In non-endemic areas, where the disease is rarely involved in the differential diagnosis, a delay in treatment may lead to severe medical complications. Due to the rising prevalence of disseminated histoplasmosis in these areas, a thorough medical history is regarded as the decisive factor in prompt diagnosis of the disease.

We, herein, report the case of an immunocompetent Greek farmer with disseminated histoplasmosis whose condition was initially misdiagnosed, and the consequential inadequate treatment led to his death.

1. Introduction

Histoplasma capsulatum is a dimorphic fungus that exists in the mycelial phase in the environment as two types of conidia: macroconidia which are approximately 8–15μm in diameter and microconidia which are 2–5μm in size and were identified as the infectious form of the disease. Microconidia are small enough to reach the terminal bronchi and alveoli; thus, after inhalation, they convert into the yeast phase within the macrophages. Generally, after inhalation, most of the patients remain asymptomatic or present with mild, self-limited symptoms. The clinical manifestations depend on the patient's age, underlying health, and most importantly immune status, as well as the size of the inhaled inoculum [1]. Clinical presentations of the disease include pulmonary histoplasmosis, mediastinal histoplasmosis, and disseminated histoplasmosis. Regarding the latter, immunocompromised patients are more likely to develop the progressive form of the disease (PDH) compared to immunocompetent patients. PDH is characterized by the progressive involvement of various extrapulmonary organ systems, mainly affecting the liver, spleen, gastrointestinal tract, and bone marrow [2]. Herein, we present a case of an apparently immunocompetent farmer in Greece with PDH. Histoplasmosis was not considered in the early differential diagnosis, therefore when the fungus was identified in a biopsy after many years it was not possible to cure the disease and the patient passed away. In Greece, histoplasmosis is not considered an endemic disease, and, to the best of our knowledge, this is the first reported case of disseminated histoplasmosis to date.

2. Case report

A 39-year-old male farmer presented to his pathologist (Day 0) with erythema nodosum (EN), arthritis of the large joints and myalgias. The diagnosis at the time was possible Reiter's syndrome and the patient was treated with corticosteroids, azathioprine and NSAIDS for 6 months. Since then, recurrence of the symptoms would happen at least three times every year, despite the pharmacological treatment. Three years later (Day +1095), he was admitted to a rheumatology department to investigate emerging cutaneous lesions on trunk, neck, upper and lower extremities which were presented right after an upper respiratory tract infection. The patient reported recurrent EN and arthritis of the large joints. After clinical examination, recurrence of erythema nodosum on

Abbreviations: EN, erythema nodosum; DH, disseminated histoplasmosis; PDH, progressive disseminated histoplasmosis; ESR, erythrocyte sedimentation rate; CNS, central nervous system; GI, gastrointestinal.

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the legs, along with papules and pustules with central necrosis on upper body were established. Skin biopsies from the lesions revealed leukocytoclastic vasculitis. Laboratory testing showed neutrophilic leukocytosis and increased levels of serum ESR and CRP. Urine testing showed microscopic hematuria, which, according to the patient, was also reported some years ago in a similar examination, without nevertheless being able to establish an exact date. The patient was tested negative for HIV-1 and HIV-2 antigens. A renal biopsy was performed four years later (Day +1460) and revealed chronic interstitial nephritis with mild mesangial hyperplasia.

In the following years, recurrence of EN, arthritis and the appearance of new skin lesions led to multiple hospitalizations. Immunomodulatory drugs were often administered, nevertheless, the diagnosis was uncertain. Six years after the patient's first visit to the pathologist (Day +2198), the disease was solely treated with infliximab, methotrexate, and methylprednisolone. Eight years later (Day +2924), the patient was admitted to the neurologic department for unsteadiness, brief episodes of dysarthria and transient loss of consciousness. Clinical examination revealed central vertigo and MRI showed periventricular leukoencephalopathy lesions. HIV serology resulted negative. A year later (Day +3288), the patient was readmitted to the neurologic clinic with right hemi-hypesthesia, and a CT scan of the brain revealed ischemic infarcts near the frontal horn of the brain and on the left of the thalamus. Throughout all these years, ESR serum levels, serum urea and creatinine levels, were also constantly elevated.

Sixteen years after the patient's first visit to the pathologist (Day +5845), flatulence, abdominal pain, high fever (38–39 °C) and increased CRP levels in the serum led to hospitalization. A colonoscopy was performed to examine the lower bowel that revealed a colon polyp and multiple ulcers in the terminal ileum and large intestine. Histopathologic examination of biopsy specimens, obtained from the terminal ileum, large intestine, and rectum, revealed severe inflammation. Many lymphocytes were observed along with clusters of histiocytes in lamina propria while numerous oval yeast forms, 2–3μm in size, were present in the cytoplasm of histiocytes (Fig. 1). These forms were stained positively with Gomori- Methenamine- Silver (GMS) and Periodic Acid Schiff (PAS) stains (Fig. 2). Serological testing for antibodies to *Histoplasma capsulatum* was positive and M band was detectable. PCR was employed and confirmed the diagnosis of histoplasmosis. After diagnosis, which was succeeded sixteen years after the first visit to the pathologist, a more detailed medical history was obtained. The patient reported that he had traveled to Central America before his symptoms for professional reasons while looking to buy agricultural equipment.

The patient was started on intravenous liposomal amphotericin B, 2 mg/kg/day for two weeks, followed by oral itraconazole 200 mg twice daily, according to IDSA guidelines. Despite the administration of antifungal agents, the patient passed away a few months later due to his clinical deterioration over the years.

3. Discussion

Histoplasmosis was first described by Samuel Darling in 1906 and, as the fungus was further studied, it was found to be highly endemic in Central and South America. It is also considered an endemic disease in Eastern Asia, Australia, and sub- Saharan Africa [3]. The rising number of immunosuppressed individuals, such as those with AIDS or those undergoing immunosuppressive treatments, has led to the global spread of this fungal infection. Cases originating within Africa and Asia have been reported as well. In Europe, most reported cases have been imported by travellers or migrants from endemic regions, though there have also been instances of locally acquired cases, particularly in Italy [4]. In Greece, histoplasmosis is not considered an endemic disease and, to the best of our knowledge, only one case of pulmonary histoplasmosis and one case of African histoplasmosis have been reported to date [5,6].

Histoplasma capsulatum is found in microfoci, especially in damp soil contaminated with bird or bat guano [1]. Therefore, agricultural activities that cause disruption of the microfoci may lead to inhalation of microconidia, the infectious form of the fungus. In our case, the patient was a male Greek farmer with no reported history of immigration or travel to endemic areas, because he was not asked during the initial assessment.

Symptomatic histoplasmosis can manifest as acute pulmonary histoplasmosis in children, chronic pulmonary histoplasmosis in older patients with prior lung damage, or disseminated histoplasmosis, which poses a significant risk to immunosuppressed individuals [7]. Our patient, who appeared immunocompetent with no known risk factors, was initially misdiagnosed and placed on immunosuppressive treatments that likely caused his clinical deterioration and death.

In an immunocompetent host, T-cell immunity is crucial for controlling the infection. Since the AIDS pandemic, PDH has been designated as a public health issue while also being one of the most common causes of AIDS-related deaths in endemic areas [8]. A deficit in cell-mediated immunity, in particular lack of Th1 response activation, result in haematogenous dissemination of *Histoplasma capsulatum* to other organs and tissues. PDH may often be the first manifestation of an HIV infection in endemic areas [9]. Our patient was tested negative twice for HIV infection, before the diagnosis of PDH was established. In our case, screening for HIV antibodies was initially performed to exclude a possible HIV-infection as the cause of patient's systemic disease.

Most patients with progressive disseminated histoplasmosis typically present respiratory and non-specific symptoms, such as fever of unknown origin and constitutional symptoms, namely fatigue, night

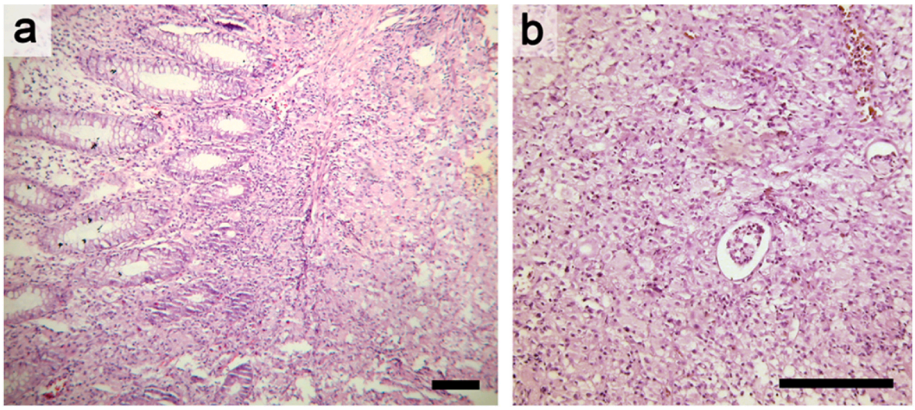

Fig. 1. Histopathological analysis of colonic mucosa reveals inflammatory infiltrations, histiocytes and presence of yeast forms. (a) Colonic mucosa is seen with its characteristic crypts. (b) An inflammatory infiltrate with abundant lymphocytes along with clusters of histiocytes is observed in lamina propria. Numerous oval yeast forms, 2–3μm in size, are present in the cytoplasm of histiocytes. Scale = 200μm.

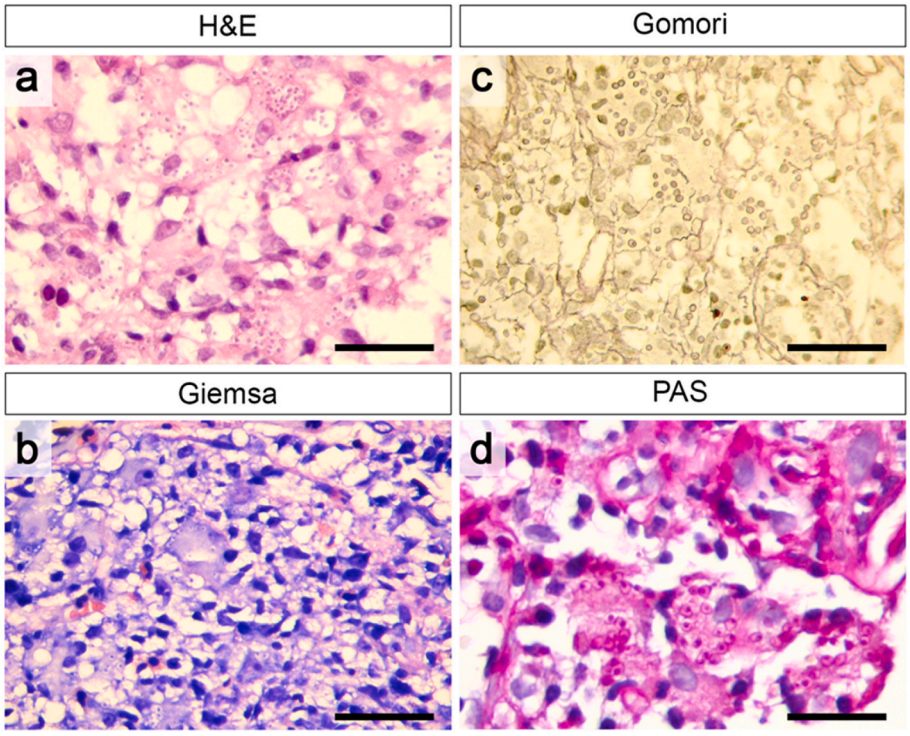

Fig. 2. Positive staining of oval yeast forms within histiocytes using various histological stains. Numerous oval yeast forms present in the cytoplasm of histiocytes are stained positively with (a) Hematoxylin Eosin, (b) Giemsa, (c) Gomori- Methenamine- Silver (GMS) and (d) Periodic Acid Schiff (PAS) stains. Scale = 100μm.

sweats and weight loss. Involvement of other organs, mainly the liver, spleen, gastrointestinal tract, lymph nodes and bone marrow are also common in PDH [2]. Besides, it has been reported that patients may exhibit rheumatologic symptoms ranging from symmetrical polyarthritis which usually affects the joints of the upper and lower extremities to EN or erythema multiform [10]. Our case appeared with recurrent EN, arthritis and skin lesions on the trunk, neck and arms, in particular red papules, and pustules with central necrosis accompanied by skin rash.

Renal involvement has been reported to be common in patients with DH, usually in the form of fungal-laden macrophages within the glomerular capillaries or the interstitium and, in most cases, those findings were not correlated with loss of kidney function. Glomerulonephritis has been described in some cases of DH, yet it is considered a very rare clinical manifestation of the disease [11]. In our case, the patient appeared with microscopic hematuria and increased serum urea and creatinine levels, while renal biopsy revealed chronic interstitial nephritis with mild mesangial hyperplasia. While these findings were not officially linked to histoplasmosis, various examinations conducted over the years did not reveal any other potential causes.

CNS involvement has been reported to occur rarely in patients with the disseminated form of the mycosis who may experience non-specific symptoms, such as fever, headaches, weakness, confusion, focal deficits, etc. Patients have been reported to develop chronic lymphocytic meningitis or, less commonly, cerebral vasculitis with stroke syndrome, encephalitis, hydrocephalous and spinal cord injuries. As the disease progresses, dysphagia, dysarthria, and bilateral facial paralysis may appear [12]. In our case, clinical manifestations from the CNS presented long after the onset of the disease and included unsteadiness, transient loss of consciousness and dysarthria, as well as hemi-hypesthesia, probably due to ischemic infarcts.

Gastrointestinal symptoms presented in later stages, the year when the diagnosis of DH was made. In an autopsy series, involvement of the GI tract was identified in 70 % of patients with DH, while symptomatic disease was solely found in 3–12 % of patients. The disease affects most commonly the ileum and, usually, it manifests with abdominal pain, diarrhoea, weight loss, vomiting, constipation, haematemesis and haematochezia [13]. Endoscopic findings include, among others, intestinal ulcerations, and polypoid masses, as in the case of our patient.

A multifaceted approach involving histological examination, serological testing, and molecular diagnostics, mainly PCR, is necessary to enhance the accuracy and timeliness of diagnosis, thereby optimizing patient outcomes; yet the gold standard for histoplasmosis diagnosis remains the isolation of the fungus in culture [14]. In our case, histological examination of biopsy specimens established the diagnosis, while serological examination and PCR were employed to confirm the mycosis.

4. Conclusion

Disseminated histoplasmosis affects patients not only in endemic, but also in non-endemic areas. The escalating incidence of PDH in non-endemic areas underscores the imperative for a comprehensive medical history, with emphasis on the patient's travelling and occupational background. Even in patients who are immunocompetent, due consideration should be given to fungal infections, particularly when a patient's response to treatment is inadequate. DH proves fatal if left untreated; hence, a heightened level of clinical suspicion, early diagnosis, and prompt initiation of treatment are paramount in preventing clinical deterioration and mortality.

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Software. **Alexandra Grekou:** Methodology, Investigation, Conceptualization. **Soultana Meditskou:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Maria Eleni Manthou:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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