Case Report / *Olgu Sunumu*

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Papiliotrema (*Cryptococcus*) *laurentii* Fungemia in an Infant with Prader Willi Syndrome

Prader Willi Sendromlu Bir Bebekte *Papiliotrema* (*Cryptococcus*) *laurentii* Fungemisi

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Abstract

Papiliotrema laurentii, previously known as *Cryptococcus laurentii*, has rarely been diagnosed as the etiological pathogen able to cause human infections. Clinical manifestations of *P. laurentii* ranges from skin lesions to fungemia. *P. laurentii* fungemia has been reported extremely rare, especially in patients with risk factors such as chemotherapy, corticosteroids, HIV infection, indwelling central venous catheter and prematurity. This study aimed to report a case of fungemia due to *P. laurentii* in an infant with Prader Willi syndrome. Despite fluconazole treatment, yeast was isolated three times from blood cultures taken one day apart. Fluconazole was switched to liposomal amphotericin B (5 mg/kg) therapy and continued for two weeks after the first report of unyielded *Papiliotrema laurentii*. The patient's clinical condition improved and was discharged home without any complication. To the best of our knowledge, this is the first case of *P. laurentii* fungemia in an immunocompetent infant.

Keywords: *Papiliotrema laurentii*, *Cryptococcus laurentii*, fungemia, pediatric

Öz

Daha önce *Cryptococcus laurentii* olarak bilinen *Papiliotrema laurentii*, son derece nadir bir insan patojenidir. *P. laurentii*'nin klinik bulguları deri lezyonlarından fungemiye kadar geniş bir spektrumda olabilir. *P. laurentii* fungemisi, özellikle kemoterapi, kortikosteroid tedavisi alan, HIV enfeksiyonu, kalıcı santral venöz kateteri ve prematürite gibi risk faktörleri olan hastalarda son derece nadir olarak bildirilmiştir. Bu yazıda *P. laurentii* fungemisi gelişen Prader Willi sendromlu bir olgu sunuldu. Flukonazol tedavisine rağmen hastadan bir gün arayla alınan kan kültürlerinde üç kez maya izole edildi. Flukonazol tedavisi amphotericin B (5 mg/kg) tedavisine değiştirildi. Kan kültüründe üreme olmadıktan sonra iki hafta daha tedaviye devam edildi. Klinik durumu düzelen hasta herhangi bir komplikasyon olmadan taburcu edildi. Bildiğimiz kadarıyla, bu immünkompetan bir bebekte *P. laurentii* fungemisinin ilk örneğidir.

Anahtar Kelimeler: *Papiliotrema laurentii*, *Cryptococcus laurentii*, fungemi, çocuk

Introduction

Cryptococcus species are encapsulated, basidiomycetous yeasts. The pathogenic yeasts of cryptococcosis are currently classified in two species: *C. neoformans* and *C. gattii*. Non-neoformans *Cryptococci*; *Papiliotrema laurentii,* previously known as *Cryptococcus laurentii*, *C. albidus* are less virulent and rarely have been reported to cause disease (1,2). However, there has been an increasing incidence of infection due to non-neoformans *Cryptococcus* spp. especially in acquired immunodeficiency syndrome (AIDS) and other immunocompromised people. Clinical manifestations of *P. laurentii* ranges from skin lesions to fungemia. We report a case of fungemia due to *Pa-*

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piliotrema (Cryptococcus) laurentii in an infant with Prader Willi syndrome (PWS).

Case Report

A five-month-old male infant diagnosed with PWS (15q11-q13 deletion) presented to the emergency department with diarrhea, vomiting and fever. On admission his temperature was 38.8°C, and tented skin, dry mucous membranes and sunken eyes were noted. Laboratory analysis revealed a white blood cell (WBC) count of 15.540/mm^3 (%72 polymorphonuclear leukocytes, %20 lymphocyte, %8 monocyte), hemoglobin (Hb) of 10.2 g/dL, platelet count of 332.000/mm^3, blood urea nitrogen (BUN) 62 mg/dL, serum creatinine 1.13 mg/dL, Na 150 mEq/L, K 3.2 mEq/L erythrocyte sedimentation rate (ESR) 26 mm/hour, C-reactive protein (CRP) 1.24 mg/dL, pH 7.16 HCO_3 9.1 mmol/L. Microscopic fecal blood and leukocytes were absent on stool analysis. Adenovirus and rotavirus antigen was negative in the stool. Stool culture was normal. Intravenous fluids and empiric ceftriaxone therapy were initiated. Seven days after admission his condition improved; however, on the 12th day of admission his temperature rose to 39°C. CRP and procalcitonin level increased to 5.51 mg/dL (<0.5 mg/dL) and 0.68 µg/L (<0.5 µg/L) respectively. Leukocytosis (WBC, 17.350/mm^3; 21% band forms), and thrombocytopenia (platelet count, 52.000/mm^3). Considering nosocomial sepsis, his therapy was changed to meropenem. In spite of this therapy the fever continued, and yeast yielded from blood culture. Fluconazole added to the meropenem therapy. Despite fluconazole treatment yeast was isolated three times from blood cultures taken one days apart. *Papiliotrema* (*Cryptococcus*) *laurentii* isolates were initially observed on Gram-stained preparations, subcultured on Sabouraud glucose agar, and identified by both carbohydrate assimilation reactions (20C AUX; bioMérieux, Marcy l ' Etoile, France), and matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, BD, Bremen, Germany) in addition to conventional methods. On microscopy, they showed spherical and elongated budding yeast-like cells with no pseudohyphae. India Ink preparation was positive for encapsulated yeast (Figure 1A and B). In vitro susceptibility tests against fluconazole, voriconazole, amphotericin B, anidulafungin and caspofungin were performed using Sensititre® YeastOne (TREK Diagnostic System, East Grinstead, UK) based on Clinical and Laboratory Standards Institute (CLSI) standards (3). The MIC values of the isolates were ≥8 mg/L for voriconazole, ≥8 mg/L for posaconazole, 2 mg/L for amphotericin B, 0.12 mg/L for anidulafungin, 0.06 mg/L for micafungin, 0.12 mg/L for caspofungin, ≥16 mg/L for itraconazole, ≥256 mg/L for flucanazole, and 0.5 mg/L for flucytosine. After *P. laurentii* had yielded in the blood culture, the patient was investigated for immunodeficiency. IgA was 34 mg/dL (5-48 mg/dL), IgG 684 mg/dL (374-789 mg/dL), IgM 99 mg/dL (29-107 mg/dL), IgE 38.5 mg/dL, and anti-HIV was negative. Fluconazole was switched to liposomal amphotericin B (5 mg/kg) therapy. A repeat culture of blood drawn on the 2nd day of therapy was negative, and the infant was weaned. Liposomal amphotericin B treatment continued for two weeks after the first report of unyielded *Papiliotrema* (*Cryptococcus*). On the third year of follow up, all immunological findings were normal including immunoglobulin levels and subclass IgG, total and subpopulations of T cells, vaccine antibody responses (pneumococcal and tetanus), complement (C3, C4, AP50, CH50). Serum TSH, free T4 level were normal, anti-nuclear antibody, anti-ds-DNA antibodies, anti thyroid peroxidase antibody, and anti-thyroglobulin antibody were all negative.

Discussion

Papiliotrema (*Cryptococcus*) *laurentii*, a basidiomycetous encapsulated yeast, is found in droppings and cloacal samples of pigeons. *Papiliotrema* (*Cryptococcus*) *laurentii* has rarely been diagnosed as the etiological pathogen able to cause human infections. *Cryptococcus* commonly invades the human body after inhalation, through the alimentary tract or injured skin. From the portal of entry, the encapsulated yeast cells are easily transported via the bloodstream to other parts of the body. Risk factors associated with *Papiliotrema* (*Cryptococ-*

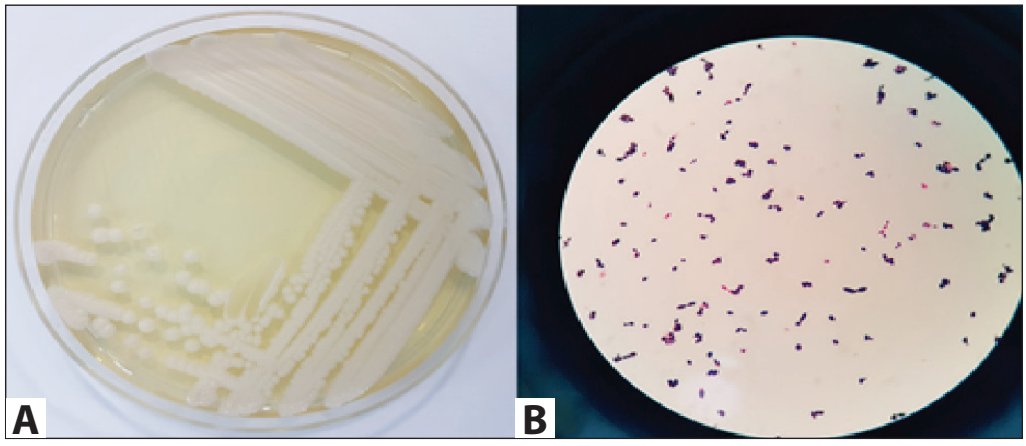

Figure 1. A.B Sabouraud dextrose agar with the colonies of *C. laurentii* and Gram stain from the same showing budding yeast cells.

cus) infection are chemotherapy, corticosteroids, HIV infection, indwelling central venous catheter (CVC) and prematurity (2). None of these risk factors were present in our patient. Most cases of non-neoformans fungemia have been nosocomially acquired and have been associated with indwelling CVC and neutropenia. Neither CVC nor neutropenia was present in our patient.

Bacteremia after bacterial and rotaviral gastroenteritis is well-documented. Candidemia complicating rotavirus gastroenteritis has been reported extremely rarely. The pathophysiology of the precise mechanisms of secondary bacteremia and fungemia during acute gastroenteritis remain unclear and probably multifactorial. It is likely that the destruction of the intestinal mucosa during acute gastroenteritis may provide a route for bacteria to enter the blood, notably in the relatively vulnerable intestinal wall of young infants (4). Although our patient did not report close contact with pigeon excreta, the cryptococcal basidiospores that have been inhaled may have been transferred to the bloodstream through the intestinal wall, whose integrity is disturbed due to gastroenteritis.

A multicenter study including 201 pediatric fungemia in a 12-year period has evaluated etiology, risk factors antifungal susceptibility and outcomes. The most detected fungus was *Candida albicans* 69.9% in neonates, in children with cancer and in ICU patients. Non-*albicans Candida* were detected in 25.1% of the patients. In this multicenter study, it has been reported that *P. laurentii* was isolated in only one patient, which is extremely rare (5).

The spectrum of clinical manifestations of *Papiliotrema* (*Cryptococcus*) *laurentii* ranges from skin lesions to fungemia. To date, there have been case reports including cutaneous, peritoneal, pulmonary, disseminated, and ocular *P. laurentii* infections. Seven cases of fungemia with *P. laurentii* have been reported previously. Two of them were premature neonate. Patients had a good outcome after the administration of amphotericin B and removal of a central venous catheter. *Papiliotrema* (*Cryptococcus*) *laurentii* that has been isolated from the blood of patients with the diagnosis of non-Hodgkin lymphoma (NHL), and acute myelogenous leukemia (AML) have been published. Patient with NHL died due to primary disease, patient with AML had a good response after amphotericin B therapy and catheter removal (1). Another case of *P. laurentii* fungemia has been reported in a young man with membranoproliferative glomerulonephritis who was on aggressive immunosuppressive therapy. He was treated with itraconazole due to septic fever, and positive microbiological blood tests continue despite fluconazole treatment (6). However, despite being extremely rare, patients with *P. laurentii* meningitis have been reported in the literature. A 59-year-old man with chronic headaches for six months has been diagnosed *P. laurentii* meningoencephalitis. The patient was HIV negative and had no immunosuppressive disorder. The only risk detected in the patient was that he was a farmer with pigeon droppings exposure. In the literature, there are four other cases with *P. laurentii* meningitis but three of them are HIV positive (7). Underlying diseases and predisposing risk factors such as chemotherapy, corticosteroids, HIV infection, indwelling central venous catheter and prematurity seem to have played an important role in these cases. However, there was no underlying risk factor in our patient. Our patient is the first immunocompetent case with *P. laurentii* fungemia with PWS reported in the English literature.

Prader-Willi syndrome results from the absence of expression of one or more maternally imprinted/paternally expressed genes in the region 15q11-q13. PWS is characterized by mental retardation, short stature, hypotonia, profound hyperphagia, obesity, small hands and feet, and hypogonadism. Dysregulation of temperature may mask infectious diseases, and some young children with PWS dying from infectious disease and/or septic shock within a very short time span from presentation have been reported. In the literature, an immunodeficiency state known by PWS has not been identified (8). Diabetes mellitus (DM) is a component of the disease and may cause immunosuppression, but our patient has no DM. In addition, immunodeficiency studies were normal in terms of accompanying immunodeficiencies.

It is reported that fluconazole-resistant *P. laurentii* has been isolated from the blood of a patient with ganglioneuroblastoma. Patient had a good response to amphotericin B treatment. Limited data on in vitro show non-neoformans cryptococci can be resistant to fluconazole and flucytosine and are susceptible in vitro to amphotericin B and several azoles, and either class of antifungal agents could be used for non-neoformans cryptococcaemia (9). We had good response with amphotericin B to recurrent *P. laurentii* yielded.

In the literature, all patients with *P. laurentii* fungemia had predisposing factor and underlying immunodeficiency. To our knowledge, this is the first report that *P. laurenti* fungemia occurred in an immunocompetent infant. Blood cultures should be obtained from children with acute gastroenteritis and persistent or recurrent fever although the rate of secondary fungemia is extremely low. Results from blood cultures may be valuable to enable the prevention of this life-threatening complication.

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