



CASE REPORT

CANDIDA ALBICANS MENINGITIS ASSOCIATED WITH INTRACRANIAL HEMORRHAGE

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SUMMARY

Invasive fungal infection is an uncommon, but increasing cause of morbidity and mortality in neonates and infants. Majority of the cases of central nervous system (CNS) candidiasis are associated with disseminated or invasive candidiasis. CNS candida infections may be caused by meningitis, microabscesses of the brain, vasculitis from fungal invasion of the vessel wall with thrombosis and secondary infarction and mycotic aneurysms with hemorrhage. In this article, a thirty-one-day old patient with candida meningitis complicated with subarachnoid hemorrhage and cerebral infarction, a very rare manifestation, is reported.

Key Words: Candida albicans, Meningitis, Subarachnoid hemorrhage.

INTRAKRANİYAL HEMORAJİ İLE İLİŞKİLİ CANDIDA MENENJİTİ

ÖZET

İnvaziv fungal enfeksiyonlar yenidoğan ve süt çocukluğu döneminde nadir ancak mortalite ve morbiditesi yüksek enfeksiyonlardır. Santral sinir sistemi candidiazisinin büyük çoğunluğu ise dissemine ve invaziv candida enfeksiyonu ile birlikte dir. Santaral sinir sisteminin candida enfeksiyonunda etkenin damar duvarı invazyonu ve trombozisi ile sekonder infarkt ve kanamalı mikotik anevrizma oluşumu menenjit, beyinde mikroabse ve vaskülit neden olur. Bu makalede oldukça nadir bir komplikasyon olarak subaraknoid hemoraji ve serebral infarkt gelişen candida menenjitli 31 günlük olgu sunulmuştur.

Anahtar Kelimeler: Candida albicans, menenjit, subaraknoid hemoraji

INTRODUCTION

The prevalence of systemic fungal infections has increased significantly during the past decade. According to surveillance studies, nosocomial candidemia now accounts for 10 - 15% of all hospital-acquired bloodstream infections¹⁻³. Neonatal candidemia occurs in 4% - 15% of extremely low birth weight infants (birth weight <1000 g), and the 30-day mortality approaches to 40%⁴.

Candida meningitis is the most frequent manifestation of invasive candidiasis - related CNS Candidiasis. Diagnosis is established by isolation of Candida sp. from cerebrospinal fluid (CSF). Scattered brain microabscesses, brain abscesses, vasculitis thrombosis and infarction are the other manifestations of CNS candidiasis⁵. Histopathologic confirmation of

vascular involvement in cases of CNS-candidiasis is well described but clinical presentation with basilar artery thrombosis and subarachnoid hemorrhage resulting from rupture of mycotic aneurysm or arteritis with vascular invasion but is seems very rare.^{5,6}

In a 31 day old patient with intact immunity and having no other risk factors, a very rare clinical manifestation candida meningitis with subarachnoid and intracerebral hemorrhage, is presented.

CASE REPORT

Previously healthy a thirty-one-day old boy, was admitted to the hospital with lethargy, irritability, inability of suction, fever and focal seizure. No previous history of predisposing factors was obtained. On

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physical examination, his weight, height and circumference of head were on the 50th percentile, axillary body temperature was 38,4°C. He was lethargic, irritable and had bulging fontanel; examination of other systems were found to be normal. Erythrocyte sedimentation rate was 58 mm/h, C reactive protein level was 9.8 mg/dl, hemoglobine level was 7.2 g/dl and blood leucocyte count was 23.300/mm³ with neutrophilic predominance. Urine examination, serum electrolytes, renal and liver function tests, prothrombin time and partial thromboplastin time were found within normal ranges. Empirical antibiotics and anticonvulsive therapies were initiated. Lumbar puncture (LP) was delayed until the patient was stabilized. Examination of LP, performed on the second day of hospitalization, showed CSF leucocyte count of 850/mm³ with neutrophilic predominance. Erythrocyte count was 750/mm³, protein level was 205 mg/dl and glucose level was 21 mg/dl.. Antigen detection tests and culture for bacterial microorganisms of CSF were found negative. Candida albicans was isolated from blood and CSF cultures, and intravenous liposomal amphotericin B (2 mg/kg/d) therapy was added to the initial therapy. As the fever continued on the fifth day of the therapy, liposomal amphotericin B was increased to 5 mg/kg/d.

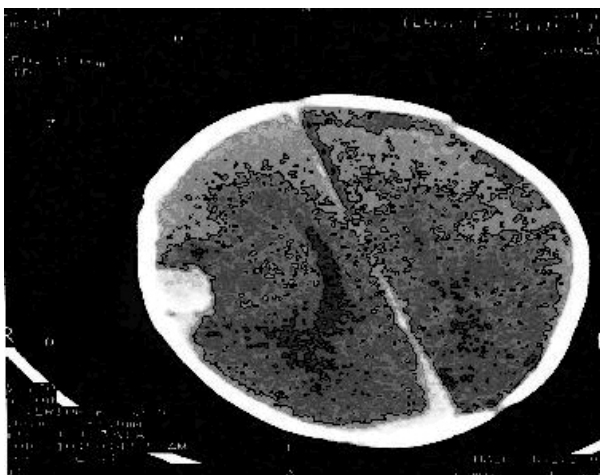


Figure1: Cranial CT showed hemorrhage on the right frontotemporal region of the brain and throughout the interhemispheric fissur

Cranial ultrasonography (USG) showed the presence of hemorrhage on the right frontotemporal region of the brain. Subsequent cranial tomography (CT) confirmed hemorrhage on the right frontotemporal region of the brain and throughout the interhemispheric fissure (Fig. 1). After neurosurgical consultation, it was decided that the patient did not need surgical drainage.

Immunologic studies of the patient revealed a normal neutrophil burst test by flow cytometry. Serum IgG and IgG subgroups, IgM, IgA, IgE levels were within normal ranges. Lymphocyte phenotyping by flow cytometry was found normal. Serology was negative for human immunodeficiency virus.

On the 10th day of liposomal amphotericin B therapy body temperature of the patient was normal and clinical improvement was obtained and no other convulsions were observed. Pleocytosis has continued and Candida albicans was isolated from CSF cultures on the 8th and 15th days of therapy. On the 20th day of therapy the CSF leucocyte count, protein and glucose levels were normal and CSF culture was found negative. Therefore, Amphotericin B therapy had been continued for 4 weeks. On the 4th week of hospitalization neurologic examination of the patient was found completely normal.

One month after hospitalization, control neuroimaging study was performed. CT findings showed encephalomalasia at the right temporomedial lobes revealing the involvement of the right medial cerebral artery (Figs. 2-3). One year after the infection, control neurologic examination was normal and CT findings showed decrease in intensity and volume loss at the right temporoparietal region and also dilatation of the right lateral ventricle secondary to the past cerebrovascular events (.Figs. 4,5).

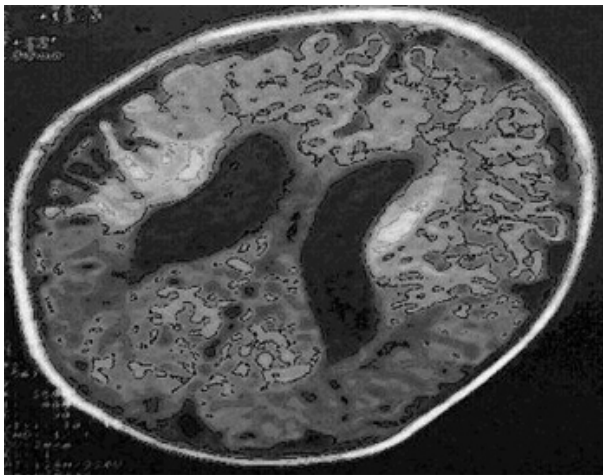


Figure 2

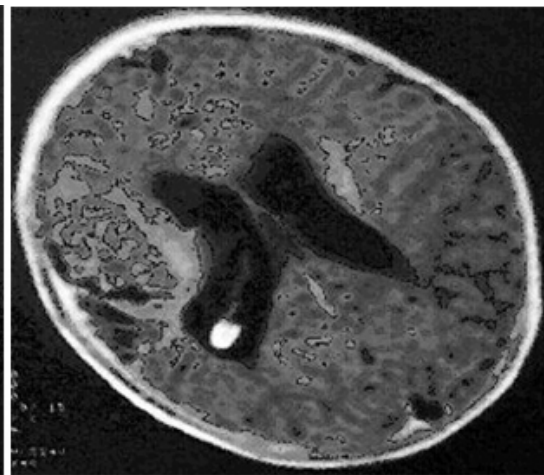


Figure 3

Figure 2-3: Cranial CT showed encephalomalasia at the right temporomedial lobes revealing the involvement of the right medial cerebral artery.

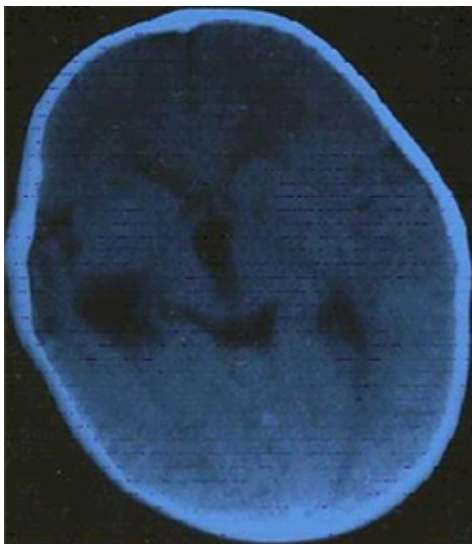


Figure 4

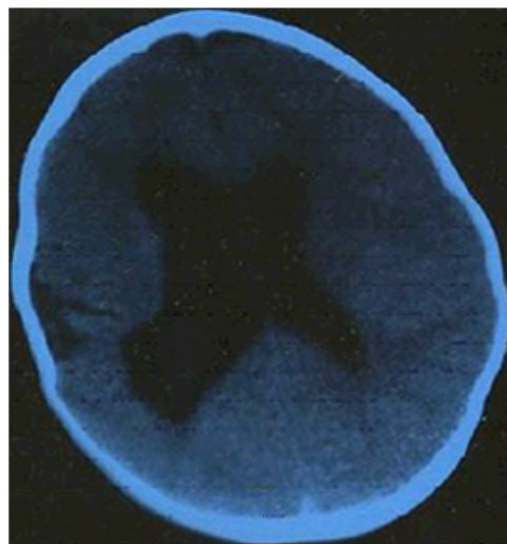


Figure 5

Figure 4-5: CT findings showed decrease in density and volume loss secondary to the past cerebrovascular events on the right temporo-parietal region and also dilatation of the right lateral ventricle.

DISCUSSION

Candida spp. can infect both the meninges and the paranchymal brain tissue. In healthy children candida meningitis rarely occurs. Our patient was admitted to the hospital with lethargy, irritability, inability of suction, fever and focal seizure and he has elevated ESR, CRP, leucocyte and decreased hgb values. Cranial USG showed the presence of hemorrhage on the right frontotemporal region of the brain. Subsequent cranial tomography confirmed hemorrhage. In

newborns with the exception of hemorrhage in posterior fossa area, surgical drainage of hemorrhage is not indicated, because of poor outcomes⁷⁻⁹. So the patient was clinically followed up.

In our patient examination of LP, performed on the second day of hospitalization, showed meningitis so empirical antibiotherapy was continued. Antigen detection test and cultures for bacterial microorganisms were found negative but his fever has continued. Although antibacterial therapy changed on the



7th day, his fever had continued for 14 days. On the 14th day, *Candida albicans* was isolated from his first CSF and blood cultures and liposomal amphotericin B was added to the therapy. Virtually all patients with candida meningitis have cerebrospinal fluid (CSF) pleocytosis. Fifty percent has a lymphocyte pleocytosis with an average count of 600 cell/mm³; sixty percent has low glucose and elevated protein levels. Typical abnormalities include CSF pleocytosis between 500-600 cells/mm³, lymphocyte or polymorphonuclear preponderance (50 % for both) moderately low glucose (60 % of the cases) and mild increase in protein levels. Organisms are positive on wet mount or gram stain in only 30-40 % of the cases.¹⁰ Also our patient had CSF pleocytosis, polymorphonuclear preponderance, moderately low glucose and an increase in protein levels.

The greater use of broad spectrum antibiotics, immunosuppressive agents, hyperalimentation products and umbilical or central venous catheters, intensive care of low birth weight infants and the acquired immunodeficiency syndrome (AIDS) are the risk factors for the development of candida sepsis. Kremery et al evaluated the risk factors in 101 cases of nasocomial bacterial and fungal meningitis in children and determined the major risk factors as in Arisoy's study¹¹. Our patient was a 31 day old boy with intact immunity and had no such risk factors.

Diagnosis was established by isolation of candida from CSF; by detection of antibodies to candida in CSF by immunodiffusion test, and from histological examination and culture of meningeal and brain biopsies¹. Isolation of candida from blood does not establish the diagnosis. *Candida albicans* was isolated from blood and CSF cultures in our patient. Arisoy reported the incidence of positive fungal culture as 2% among 1498 patients with positive CSF cultures².

Clinical patterns of CNS candida infections, in approximate order of frequency are candidal meningitis, brain abscess and granuloma^(12,13). Brain abscesses are rare, with the reported overall incidence in patients with disseminated candidiasis ranging from

below 1- 2%; however, various autopsy series have put the incidence as 7 - 17%. In a multicentre prospective study, culture-positive meningitis was reported as 16%, central nervous system invasion such as ventriculitis and brain parenchyma abscesses was 4%. They found that the proportion of infants who were infected with *C. albicans* was linked with an increase in meningitis. They suggest routine examination of the CSF in all neonates with candidemia because the data have both prognostic and therapeutic significance⁴. Hydrocephalus is a frequently occurring complication. Rarely vasculitis from fungal invasion of the vessel wall with thrombosis and secondary infarction, mycotic aneurysms with hemorrhage have occurred^{1,5}. Grimes et al reported vasculitic basilar artery thrombosis in a woman with chronic candida meningitis.¹⁴ Rabah R et al presented an 11 month old child with acquired immunodeficiency syndrome and candida meningitis which was accompanied by basilar inflammation and fibrosis of meninges with arteritis, vascular invasion by fungi, and terminal subarachnoid hemorrhage.¹⁵ Dufner F et al reported a 27 year old patient with intact immunity and chronic candida empyema in the craniocervical junction with recurrent epidural bleedings¹⁶. In our patient, rupture of middle cerebral artery due to severe arteritis was thought to be the cause of this hemorrhage. In literature, the clinical presentation of CNS candidiasis with basillary artery thrombosis and subarachnoid hemorrhage resulting from rupture of mycotic aneurysm or arteritis is very rare especially in clinical presentation with intact immunity^{5,6}.

In disseminated candidiasis; amphotericin B or fluconazole are used for therapy. Some offer fluconazole and amphotericin B combination therapy^{1,17-21}. The combination of amphotericin B plus fluconazole has been reviewed recently by Sugar²² it was found no antagonism between amphotericin B and fluconazole and the activity of the combination yielded a slightly greater reduction in colony-forming units compared to fluconazole alone¹⁹. Although amphotericin B penetrates the CSF of the



neonate more efficiently than the adult patient, doses of <1 mg/kg/d amphotericin B are not sufficient for the treatment of Candida meningitis⁴. We used liposomal amphotericin B in doses of 2 mg/kg/d and no side effect has been reported. Because his fever continued at the fifth day of antimicrobial therapy, the dose of liposomal amphotericin B was elevated to 5 mg/kg/d. In our patient, fever is decreased at 10th day of therapy so that we used liposomal amphotericin b alone. When fluconazole is used for systemic candidiasis, the initial dose is 400-800 mg (8-12 mg/kg per day), followed by 200 mg per day (4 to 6 mg/kg per day). During fluconazole therapy serum creatinine and transaminase levels may be elevated and thrombocytopenia may occur.^{17,21} Flucytosine is not effective when used alone, and is only used in combination with amphotericin B and fluconazole.¹⁹ New triazoles with broad-spectrum antifungal activity, such as saperconazole, are also being assessed, but clinical studies had been discontinued because of superconazole-associated tumors in laboratory animals.

The duration of treatment with amphotericin B and fluconazole range from 4 to 6 weeks according to various reports. Definitive duration of therapy has not been documented. Therefore many investigators offer to continue the therapy 3-14 days after the first negative CSF culture was obtained. Our patient was given amphotericin B for 4 weeks, pleocytosis of CSF has been continued for 2 weeks and no side effects was observed during amphotericin B therapy²⁰⁻²³.

The mortality rate was reported to be 6-50% in various studies, mortality rates were found higher in fungal meningitis, but no statistically difference was found between sequela of fungal and bacterial meningitis^{19,24}.

As a result this patient emphasizes that systemic candidiasis and candida meningitis should be considered even in patients with no predisposing risk factors for candidiasis. The physicians should also be aware of the development of a rare complication, intracranial hemorrhage accompanying systemic candidiasis.

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