

# Disseminated *Candida albicans* infection in an immunocompetent host

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## ABSTRACT

*Candida albicans* (CA) is an opportunistic fungus, which lives in close association with its human host. Immuno-competence is the barrier to its tendency to invade. Normal skin, commensal bacteria and neutrophils are the first hurdles and once broken down by indwelling catheters, antibiotics or ablative chemotherapies, dissemination can occur with grave consequences. We describe a young patient with apparent full immune competence, who suffered from disseminated CA infection, her presentation, diagnosis and therapy with amphotericin B deoxycholate, which led to her complete recovery and return to a productive life.

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Studies have revealed that *Candida albicans* (CA) species has a high pathogenic potential owing to their ability of differential expression of virulence factors at each stage of penetration of underlying tissues.<sup>1</sup> Disseminated infections most commonly occur when the normal defense barrier of the skin is breached or the immune system is compromised as in the setting of indwelling catheters, organ transplantation, prolonged antibiotic therapy, and human immunodeficiency virus infection.<sup>2</sup> In our report, we present a young immuno-competent female of African origin, who developed a disseminated *Candida albicans* (DCA) infection; her initial symptoms, diagnosis and management and return to healthy state. This report highlights the versatility of the organism to escape the bodies' natural immune components.

**Case Report.** An 18-year-old Sudanese female presented to the accident and emergency department, Riyadh Medical Complex, Riyadh, Kingdom of Saudi Arabia complaining of malaise for 5 months. Two months before admission she had

developed loss of appetite, nocturnal fever, weight loss, amenorrhea, swellings in the neck and a swelling in the center of her forehead and pain with swelling over the shaft of her left leg. First, she felt generalized weakness when nocturnal fever developed causing drenching night sweats. She then noticed a bulging swelling over her forehead, which was followed by a cervical lymphadenopathy. Finally, she started to have an aching pain in her left lower leg with a small swelling over the painful site. She had lost 8 kg over the previous 2 months. At the first health care center she visited a month earlier she was diagnosed to have "anemia" and "giardiasis" and was given supplemental iron and a course of metronidazole for 7 days without improvement. Two weeks prior to admission she sought help at another private clinic and was diagnosed as a case of "iron deficiency anemia" and "occult infection" and was started on cefuroxime for one week yet the fever did not abate.

History revealed that she had been a full term vaginal delivery, had been fully immunized and had had no major childhood illnesses, with no hospital

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admissions or blood transfusions. She achieved her menarche at the age of 15 years and suffered from dysmenorrhea since. She was single and denied any sexual activity. She was a high school girl in her final year with a history of travel only to her home country of Sudan 2 years earlier. There was no family history of diabetes mellitus, and apart from her father and her paternal uncle who both suffered from primary epilepsy her mother and 4 other siblings were well. There was no history of animal contact or pets. She denied having had malaria, and there was no history of exposure to tuberculosis.

On physical examination she was emaciated with discrete small tender lymph nodes in the posterior cervical triangles, a cystic forehead swelling with bony margins 2 x 2.5 cm in size without discoloration or change in the temperature of the skin, and a small 1 x 1 cm similar tender swelling over the mid-tibial area anteriorly. Her vital signs revealed a temperature of 38°C, a pulse of 98 beats/minute, a blood pressure of 100/70 mm Hg and a respiratory rate of 21 breaths/minute. Examination of the chest, cardiovascular system, abdomen, pelvis and central nervous system were normal. Urinalysis showed albumin nil, glucose nil, acetones nil, specific gravity 1030. Initial laboratory investigations showed a complete blood count revealing a white blood cell count (WBC) of  $8.6 \times 10^9/L$  with a differential count of neutrophils 60.2%, lymphocytes 26.3%, monocytes 5.8%, eosinophils 7.3%, and basophils 0.3%, hemoglobin 9.3 g/dl, hematocrit 29.7%, mean cell volume 77.8 fl, mean cell hemoglobin 24.4 pg, mean cell hemoglobin concentration 31.4 g/dl, and a platelet count of 180. The coagulation profile was normal. Hemoglobin electrophoresis revealed a normal pattern. Erythrocyte sedimentation rate was 84 mm/hour. Malaria films, thin and thick films repeated 3 times, were negative. Urea and electrolytes, fasting glucose level, lactate dehydrogenase level, creatinine kinase level, bone profile and lipid profile were normal. Liver function tests were normal apart from a low level of albumin 28 g/l, and a high level of total protein 90 g/l. Blood and urine cultures were negative for bacteria or fungi. Chest radiograph was normal.

On admission, she was started on ceftriaxone 2 grams intravenously (IV) once a day and the following day had aspiration of her forehead swelling from which 5 ml of frank pus was removed and sent for analysis. An orthopedic consult was made in view of her tibial swelling and when she remained highly febrile with temperatures reaching 39.5°C, clindamycin 600 mg IV every 8 hours was added on the third day of hospitalization. Cervical lymph node fine needle aspiration was performed and showed only reactive hyperplasia. Bone marrow aspiration and trephine biopsy showed a picture

compatible with anemia of chronic illness, active hematopoiesis and no evidence of an infective or malignant process. Stains and cultures of the bone marrow aspirate were negative for tuberculosis or fungi. Due to the presence of amenorrhea, hormonal tests were ordered, and a thyroid profile, follicle stimulating hormone, luteinizing hormone, and prolactin levels were normal. Ultrasound of the abdomen and pelvis did not reveal organomegaly or evidence of lymphadenopathy. When an x-ray of skull revealed a well-defined erosive frontal lesion a computed tomography (CT) of the brain and skull (**Figure 1**) was ordered to define any intracranial extension, the study however showed a small lytic lesion seen in the frontal bone eroding the undertable of the cranial vault with a small soft tissue elevation in the scalp. No intracranial extension was noted. Neutrophils showed strongly positive myeloperoxidase activity. Total protein electrophoresis showed a high gamma globulin fraction of 37.7%. Immunoglobulin (Ig) electrophoresis revealed normal IgA and IgM levels with elevated IgG of 25.7g/l (normal range [nr]: 8-18 g/l). A Paul-Bunnell test was negative, so were *Brucella melitensis* and abortus titers. Epstein-Barr virus IgG was positive and IgM negative. Cytomegalovirus IgG was 0.87 IU/ml and IgM was negative. A connective tissue screen showed a negative rheumatoid factor, twice negative antinuclear antibody and double stranded DNA antibody. Complement levels were in the upper normal range, C3 120 mg/dl (nr: 52.6-120 mg/dl), C4 47.3 mg/dl (nr: 20.5-49 mg/dl). Screens for HIV 1 and 2, and human T cell lymphotropic virus 1 (HTLV 1) were negative. Immunopheno-typing of lymphocytes revealed normal results with a WBC/ $\mu$ l of 7500, lymphocytes 28.9%, absolute lymphocytes/ $\mu$ l 2168: T lymphocytes (Cluster Designation [CD] 3+) 85% total count/(TC/ $\mu$ l) 1842 reference range (Rf) (62-76%). B Lymphocytes (CD 19+) 9% TC/ $\mu$ l 195 Rf (7-19%), natural killer lymphocytes (CD16+, CD56+) 9% TC/ $\mu$ l 195 Rf (9-23%), T helper lymphocytes (CD 3+, CD4+) 43% TC/ $\mu$ l 932 Rf (27-45%), T suppressor lymphocytes (CD3+, CD8+) 31% TC/ $\mu$ l 672 Rf (26-44%), T Helper/Suppressor ratio (CD3, CD4/CD3, CD8) 1.39 Rf (1-1.6). Phagocytosis (respiratory burst) was normal on whole blood assay. Isolated phorbol 12-myristate 13-acetate assay and a phagocytic index was normal. Aspiration of the forehead swelling grew CA. Both from the lymph-node and bone biopsy of the left tibia *Candida* species were isolated with the bone biopsy showing a granulomatous lesion with many foreign body giant cells containing fungal (yeast form) organisms (**Figure 2**). Subsequent fungal culture confirmed the diagnosis further. The Mannan antibody level was not available to the

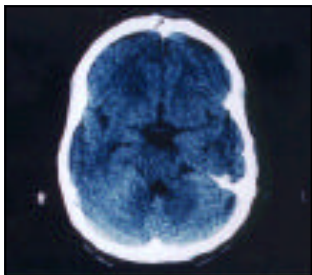


Figure 1 - Computed tomography scan of the brain showing a well defined erosive frontal bone lesion.

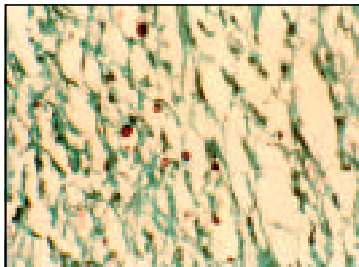


Figure 2 - Bone biopsy specimen revealing yeast forms of *Candida albicans* within the bone matrix.

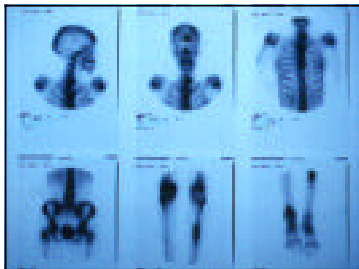


Figure 3 - Technetium 99 MDP bone scan showing multiple foci of abnormal tracer fixation especially on the forehead and long bones of lower limbs.

treating team. Bone radiograph of the left tibia revealed an osteolytic mid-shaft lesion. A CT of the neck and dorsal spine with contrast was normal. Technetium 99 MDP bone scan (Figure 3) revealed multiple foci of abnormal tracer fixation indicating multiple active bony lesions in the skull, cervical spine, dorsal spine, mid-shaft of the left tibia, lower right femur and lower right tibia.

Based on the above biopsy results and the earlier finding of CA in the forehead aspiration, a diagnosis of disseminated systemic candidiasis was made and the patient commenced on amphotericin B deoxycholate (ABD) on the 25th day of hospitalization. After the conventional test dose of 1 mg of ABD the dose was increased daily by 0.1 mg/kg to reach the therapeutic dose of 0.5 mg/kg/day and then continued until discharge. The patient was pre-medicated with paracetamol, and hydrocortisone 25 mg was added to the solution of ABD prior to each administration. The patient became afebrile on the 8th day following initiation of ABD therapy, and her weight steadily increased from 30 kg on admission to 35 kg upon discharge. Potential hypokalemia from ABD was averted by a small dose of the potassium sparing diuretic triamterene. There was only a transient rise of her creatinine during the 80 days of her confinement, which did not necessitate abortion of therapy. The erythrocyte sedimentation rate a week prior to discharge had decreased to 10 mm/hour. Upon discharge, she had received a total dose of 1.2 grams of ABD and after consultation with the orthopedic surgeons, she was to receive a total of 3 grams as twice weekly administrations due to the well-known poor penetration of ABD into bone. Six years later, on a follow-up visit, she is in good health and has completed her college education with no further episodes of fungal or other infections.

**Discussion.** *Candida albicans*, Latin for "the shining white," is a fungus designated as a commensal organism, namely, a life form existing along another life form without mutual benefit.<sup>3</sup> It has now been recognized that CA has emerged as a common pathogen. Normal defense mechanisms once breached, naturally as in diabetes mellitus or iatrogenically by an indwelling catheter, allow CA to assume this role.<sup>2,4</sup> Disseminated *Candida albicans* infections on the most part are due to iatrogenic causes, the most important being the introduction of antibiotics and the widespread use of indwelling intravenous catheters.<sup>2</sup> In addition, candidemia occurs in cancer patients, whether they suffer from solid or hematogenous malignancies.<sup>5</sup> Gastrointestinal surgery is another, well recognized risk factor for DCA.<sup>6</sup> Immunosuppressed patients, and in particular neutropenic patients, remain at the

high risk for DCA.<sup>7</sup> However, there have been reports of DCA in immuno-competent patients.<sup>8,9</sup>

Our patient presented with symptoms of a systemic illness characterized by a nonspecific fever, anorexia, malaise, amenorrhea and lymphadenopathy. She was unusual in her presentation since she lacked any history of immunosuppression, hospitalization, intravenous drug abuse or risk factor for a human immunodeficiency viral infection, and on physical exam no oral thrush or intertrigo could be detected. The swelling in the forehead was subcutaneous and was unusual in its size, as cutaneous lesions of disseminated CA usually are macro-nodular and only 0.5-1 cm in diameter.<sup>10</sup> The involvement of her left tibia reaffirmed the established fact, that in children the long bones are usually affected compared to adults.<sup>2</sup> However, the bone scan indicated a much wider involvement of both the axial and peripheral skeleton, which might point out the fact that our patient was at the watershed between child and adulthood. The areas over the underlying osteomyelitis presented as a tender swelling.

Diagnosis proved to be easy once aspirated material from the forehead swelling was cultured, since CA grows easily on ventilated blood agar and does not need special fungal culture media.<sup>2</sup> Dissemination was confirmed when examination of the bone biopsy showed CA in the yeast form. Again, as has been observed previously in many patients with disseminated disease, blood cultures for CA were negative.<sup>2</sup> Treatment was commenced with ABD, since it is established, was available and studies of its liposomal derivatives in candidiasis were not yet completed.<sup>11</sup> Apart from mild renal impairment the treatment course was uneventful.

The question remained of how an apparently healthy girl could develop such a disseminated illness. Could the received initial antibiotic treatment have resulted in esophageal candidiasis and subsequent invasion, since the gastrointestinal tract is thought to be a possible portal of entry.<sup>12</sup> Immunity is the freedom from pathogenic organisms and develops in part from an interaction between the host's defenses and his environment.

But, it is not a static condition and there are ill understood constitutional factors, which make one species innately susceptible and another resistant to certain infections.<sup>12</sup> This statement by Professor Roitt<sup>12</sup> can in our opinion be extended to the individual as it could have been the case in our patient.

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