Hepatosplenic Candidiasis in Patients with Acute Leukemia

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Citation

Abstract
Hepatosplenic candidiasis (HSC) or chronic disseminated candidiasis (CDC) is an invasive fungal infection that affects neutropenic patients. The Invasive Fungal Infectious Group of the European Organization for Research and Treatment of Cancer (EORTC-IFIG) and the Mycoses Study Group of the National Institute for Allergy and Infectious Diseases (MSG-NIAID) require peripheral, target-like abscesses on liver and/or spleen imaging in addition to elevated serum alkaline phosphatase levels for diagnosis of HSC [1]. Despite this standardized definition, consistent data yielding an estimated incidence is not yet available.

EPIDEMIOLOGY
Universal incidence of HSC has not been assessed by any published studies. Anttila et al diagnosed HSC in 6.8% of 562 patients with acute leukemia using histologic examination and imaging criteria [2]. Blade et al reported 3.1% incidence of HSC in a study involving 305 leukemic patients [3]. Chen et al reported a probable diagnosis of hepatosplenic fungal infection in 37 of 500 adult leukemic patients. Fourteen of those 500 patients (2.8%) were conclusively diagnosed with HSC [4]. The wide range of purported incidence by these case reports may reflect the lack of standardized diagnostic criteria in the past. The definition of HSC by EORTC-IFIG and MSG-NIAID was employed by Chen et al and will likely lead to better epidemiological data in the future [1, 4]. This definition combined with DNA analysis and new laboratory identification techniques may allow for easier diagnoses and improved detection rate [1, 4]. The numerous case reports in the literature have provided clear risk factors associated with the development of HSC.

RISK FACTORS
The most unvarying risk factor is a prolonged neutropenic state [1, 4]. Therefore, patients with acute leukemia following chemotherapy and patients with profound immunodeficiency have been the most frequently reported cases of HSC [3, 4, 18-21]. There are very few published cases of HSC infection in non-neutropenic patients, although one patient with no apparent immunodeficiency has been reported [4].

The classification of leukemia does not appear to affect the risk of infection. Chen et al reported 1.6% incidence of hepatosplenic fungal infections in patients with acute lymphoblastic leukemia (ALL) and 5.8% incidence in patients with acute myeloid leukemia (AML) [4]. In contrast, Anttila et al reported 11.3% incidence of HSC in patients with ALL and 5.1% incidence in patients with AML [2]. The chemotherapeutic plan instituted may actually affect the risk of infection more than the underlying leukemic condition. In a retrospective analysis of 51 patients with acute leukemia, Woolley et al determined that augmenting the dose of cytosine arabinoside increased the risk of HSC [14]. Mucositis of the gastrointestinal tract may account for this observation. One hypothesis for the pathogenesis of HSC affirms that movement of Candida species through damaged mucosa into systemic and portal circulation may lead to seeding of the liver and spleen [4]. However, no concrete data exists to support this hypothesis at this time.

MICROBIOLOGY
Candida species are fungal opportunistic pathogens that are normally present in human and animal flora. Candida albicans is especially ubiquitous, usually being found as a component of the normal microbiologic community within the gastrointestinal, respiratory, and genitourinary tracts. The strict aerobic nature of Candida albicans allows for easy acclimatization to the host mucous membranes.

Candida albicans has been a frequently reported species causing HSC [19,20,21]. However, it is clear that a wide variety
of Candida species may also be detected. D’Antonio et al and Kirby et al both reported cases of HSC caused by Candida parapsilosis [6, 12]. Chen et al identified Candida tropicalis, Candida albicans, Candida parapsilosis and Candida krusei in 14 patients with acute leukemia. Candida tropicalis was found in 6 of 14 (43%) patients, while Candida albicans was identified in 2 (14%) patients, Candida parapsilosis in 1 (7%) patient and a Candida parapsilosis and Candida krusei mixed infection in 1 (7%) patient [6]. Many pathogens among the Candida species may account for hepatosplenic infection evidenced by the variety of organisms implicated in the literature. The endemic prevalence of a certain Candida species may possibly influence the infection rate in a mode not yet elucidated.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

The vague presentation of HSC adds to the difficulty of accurately diagnosing the condition. The most commonly reported symptom is fever unresponsive to antibiotic treatment [1, 7±9±12±17±17±17±22±3±24±25±26±27±28±29±30]. The fever commonly presents following induction or consolidation treatment [11]. Abdominal pain has been frequently reported as well [26±26±30±30]. Patients may also present with nausea, vomiting or anorexia [17±27±29±30].

Blood cultures and histological examination of tissue biopsies are generally considered the “gold standard” for absolute diagnosis of HSC. Unfortunately, both these modalities of identification suffer from major limitations. Blood cultures lack sensitivity and may require long incubation times, while tissue biopsy in thrombocytopenic and neutropenic patients increases morbidity [12]. Tissue biopsy does provide excellent diagnostic clues for identification. Histological examination of samples with HSC lesions demonstrates yeast and pseudohyphae in a microabscess formation [12].

Newer techniques involving DNA analysis may aid in the diagnosis of HSC. Polymerase chain reaction (PCR) restriction enzyme analysis of the serum is sensitive and has a high negative predictive value [12]. Kirby et al utilized PCR in examination of serum and tissue samples from a patient with AML confirming the diagnosis of hepatosplenic Candida parapsilosis infection. In this case, biopsy DNA analysis was proven to have a higher sensitivity as compared to serum DNA analysis [11].

Mannan, an antigenic cell wall component of Candida species, has recently been investigated for usefulness in the diagnosis of HSC. Prella et al reported 89% sensitivity, 84% specificity, 86% positive predictive value and 88% negative predictive value when using assays for mannan antigenemia in combination with antimanann antibodies. The time required for diagnosis using these assays was also found to be shortened when compared to imaging techniques [17]. Specific laboratory abnormalities do not present consistently in patients with HSC. EORTC-IFIG and MSG-NIAID mandate that an elevated alkaline phosphatase level be present for diagnosis of HSC [11]. Although elevation of alkaline phosphatase is an abnormality noted in many case reports, the lack of specificity hurts its overall value in diagnosis [15]. Anttila et al noted a markedly increased level of serum C-reactive protein (CRP) in a retrospective study of 26 patients with HSC [11]. However, an elevated serum CRP level, akin to an elevated alkaline phosphatase level, is remarkably nonspecific.

**IMAGING**

Imaging is essential for both diagnosis of HSC, as well as appraisal of treatment efficacy. Traditionally, ultrasound and abdominal computed tomography (CT) have been used to evaluate patients with suspected HSC. Ultrasound has been proven to lack sensitivity in the identification of HSC lesions. Abdominal CT is superior to ultrasound in this regard [15]. Pastakia et al suggested using ultrasound in combination with abdominal CT to maximized sensitivity [11].

Magnetic resonance imaging (MRI) appears to be superior to both abdominal CT and ultrasound for diagnosis of HSC and evaluation of treatment progress [15]. In a comparative study between MRI and abdominal CT in 11 patients with suspected or proven HSC, Semelka et al demonstrated that MRI was superior to CT in the identification of both acute and treated candidal lesions [11]. MRI has been shown to have excellent diagnostic capability. In one prospective study, MRI was determined to have a sensitivity of 100%, specificity of 96%, positive predictive value of 85% and negative predictive value of 100% in patients with acute presentations of HSC [11]. Non-invasive monitoring of treatment progression is also possible with MRI. In 15 patients with proven HSC, Sallah et al repeated MRI examinations of patients at 2 weeks, 6 weeks and monthly intervals thereafter. Alteration of the lesions occurred throughout treatment, with disappearance of the lesions occurring in a median time of 9 weeks [11]. Therefore, evaluation of treatment response is possible and beneficial.
with MR imaging.

HSC lesions have a characteristic appearance on MRI, CT and ultrasound. EORTC-IFIG and MSG-NIAID describes the appearance as small and target-like located in the liver or spleen [1]. The lesions have also been described as “wheels within wheels” and “bull’s eye lesions” [17, 35]. The MRI appearance changes depending upon the phase of treatment. Acute, non-treated HSC lesions are microabscesses that appear round, small (<1 cm) and hyperintense on T2-weighted images. Treatment responsive lesions are larger with an enhancing peripheral ring and non-enhancing central region. Healed lesions are irregularly shaped measuring from 1-3 cm [15].

**TREATMENT AND PROGNOSIS**

Treatment for HSC has largely been based on observational data from published case reports. No randomized, controlled trials have been performed to compare the various treatment options. The Infectious Disease Society of America (IDSA) recommends fluconazole (6mg/kg per day) for clinically stable patients, and amphotericin B deoxycholate (0.6-0.7 mg/kg per day) or liposomal amphotericin B (3-5 mg/kg per day) for acutely ill patients or patients with refractory HSC [16]. The endpoint of therapy is variable and should be considered in the clinically asymptomatic patient with documented resolution of hepatosplenic lesions by imaging. Chemotherapy should not be interrupted in patients with HSC receiving concurrent antifungal therapy [16].

Caspofungin may be an option for therapy in refractory cases of HSC. Amphotericin B and azole resistant Candida species adequately treated with caspofungin (50 mg per day) has been reported [17].

Prophylaxis during neutropenic or anticipated neutropenic states is essential for decreasing the incidence of HSC [16]. The IDSA recommends fluconazole (400 mg per day) or itraconazole solution for those at risk of neutropenia for prophylaxis against invasive candidiasis [15]. These recommendations are partially based on a randomized controlled trial of fluconazole (400 mg per day) for fungal prophylaxis versus placebo in 274 neutropenic patients. The study resulted in fewer invasive fungal infections for patients with fluconazole prophylaxis (6.3%) compared to patients treated with placebo (24%) [16]. The duration of prophylaxis should cover the expected period of neutropenia. However, due to variance in chemotherapeutic regimens, prophylaxis should be customized for each patient because the risk of invasive candidiasis is not equivalent among all protocols [16].

The prognosis of HSC in adult patients with acute leukemia is not easily determined due to the severe comorbidities required for development of the condition. The IDSA recognizes the chronicity of HSC, but states that it is not acutely fatal [15]. Pagano et al also reported that HSC is not acutely fatal as a complication of malignancy [35]. Chen et al reported that in a population of 37 patients with probable and proven hepatosplenic fungal infections, 7 of the 23 patients (30%) that died were due to the invasive fungal infection [1]. The percentage of these fungal infections that were of Candida species is unclear. Although absolute prognostic implications of HSC are not well defined at this time, it is clear that patients with acute leukemia complicated by HSC have a high mortality rate.

**CONCLUSION**

HSC is a condition that affects the severely immunocompromised population of acute leukemic adults. The most widely accepted risk factor is a prolonged neutropenic state. Exact incidence is unknown, but HSC appears to be relatively common. The most frequently isolated species is Candida albicans, although endemic organisms may account for higher rates of infection depending upon location. Diagnosis of HSC is difficult due to the vague symptomatology and the lack of specific laboratory abnormalities. Imaging, especially MRI, provides important diagnostic clues and allows for monitoring of treatment progression. Proper treatment involves both antifungal therapy and prophylaxis for patient populations that may be at risk. Clinical awareness of HSC and aggressive therapeutic management is essential for improving prognosis.

**References**


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using liposomal daunorubicin and fluconazole.


Author Information

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