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Invasive fungal disease presenting as septic shock in immunocompromised pediatric and adult patients: summary of reported cases

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Abstract

Introduction: Septic shock is a very rare presentation of invasive fungal disease (IFD) in immunocompromised patients. The objective of this paper was to summarize reported cases of pediatric and adult patients with IFD presenting as septic shock in non-*Candida* infections. Literature data describing etiology, age, and outcome of septic shock as a presentation of IFD, is summarized.

Material and methods: The available pediatric data included 23 patients, most of them with underlying non-hematological disease.

Results: Only 6/23 (26.1%) were reported to survive this infection. Respective data in adults with invasive fungal disease presenting as septic shock were reported in 28 patients. Most of these patients were treated for acute leukemias (including three patients after hematopoietic cell transplantation); only 5/28 (17.9%) survived the infection.

Conclusion: Invasive fungal disease presenting as septic shock in immunocompromised patients is a highly unusual presentation.

Key words: invasive fungal disease, septic shock, hematopoietic cell transplantation, leukemia

Introduction

Patients after allogeneic hematopoietic cell transplantation (allo-HCT) belong to a high-risk group of invasive fungal disease (IFD) [1]. The distribution of pathogens in an allo-HCT setting include aspergillosis in 55–60%, candidiasis in 25–30%, mycormycosis in 7–8%, and rare species e.g. fusariosis, scedosporiosis, geotrichosis in 2–3% [2]. With the widespread introduction of antifungal prophylaxis with azoles, this epidemiology is tending to change, with the rise of rare and sporadic species. No major differences in etiology between children and adults have been reported [3–6], although in one study the incidence of IFD after allo-HCT was significantly higher in children than in adults [6]. Regardless of age, the following groups of patients are considered as high-risk groups for IFD: acute myeloblastic leukemia (AML); recurrent acute leukemia; allogeneic hematopoietic stem cell transplantation; and high risk acute lymphoblastic leukemia (ALL) [4, 5, 7–9]. Coexisting cytomegalovirus replication increases the risk of fungal complications [9].

Clinical symptoms of IFD in immunocompromised patients are dependent on the localization of the infection, which in most cases involves the lungs, abdomen, paranasal sinuses, skin or brain. In most cases, general symptoms occur including fever, followed by other systemic symptoms and laboratory markers of severe infection (e.g. C-reactive protein, procalcitonin). Sometimes, symptoms of septic shock can occur. Fungemia or fungal sepsis might occur in a case of bloodstream infection with *Candida*; nonetheless septic shock is an infrequent presentation [10]. The objective of this paper was to analyze a series of cases of pediatric and adult patients with non-*Candida* IFD presenting as septic shock.

Material and methods

Studies and case reports regarding non-*Candida* invasive fungal disease presenting as septic shock in pediatric and adult patients were searched for in ‘PubMed’. Search queries included ‘invasive fungal disease’ OR ‘invasive fungal infection’ AND ‘septic shock’. The following data was retrieved from these reports: number of patients, age, gender, underlying disease, identification of fungal etiology, antifungal therapy, and treatment outcome.

Papers were included into analysis according to the diagnosis made by the respective authors. No additional judgment of sepsis and/or septic shock was made. According to the Third International Consensus Definitions for Sepsis and Septic Shock, sepsis was defined as ‘life-threatening organ dysfunction caused by a dysregulated host response to infection’ [11]. Septic shock was defined as ‘a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone’.

Patients with septic shock can be clinically identified by the presence of two factors: the need to use a vasopressor and increased serum lactate concentration despite adequate volume resuscitation [11].

Results

Literature data describing etiology, age and outcome is very limited. The available pediatric data includes 23 patients, most of them with an underlying non-hematological disease (Table I) [12–22]. Only 6/23 (26.1%) are reported to have survived this infection, including 2/5 with acute leukemia. Etiology of the infection was highly variable, however infection with *Saprochaete spp.* (formerly *Geotrichum spp.*, now proposed as *Magnusiomyces spp.*) presenting as septic shock was reported in four children, all with acute leukemias. Only two of them survived the infection. IFD-related non-*Candida* septic shock was reported also in 28 adults (Table II) [21, 23–40]. High mortality has also been observed in adults, with only 5/28 (17.9%) patients surviving.

Table I. Literature data on septic shock in children with invasive fungal disease

Source	**Age**	**Primary disease**	**Etiology**	**Treatment**	**Outcome**
Zeng et al., 2021 [12]	Median age 22 months; age range: 3–44 months in 12 children	Various	*Talaromyces marneffei*	Amphotericin B 7/11 Itraconazole 2/11 Fluconazole 2/11 Voriconazole 3/11 Caspofungin 3/11	Died 9/12 Cured 3/12
Romanio et al., 2017 [13]	1-year-old boy	Down's Syndrome in postoperative period of congenital cardiac disease correction	*Saccharomyces cerevisiae*	Amphotericin B	Alive
Watson et al., 2016	12-year-old girl	Juvenile idiopathic	*Blastomyces*	Amphotericin B, adjunctive inhaled	Died

[14]		arthritis		amphotericin; liposomal amphotericin B was changed to amphotericin B lipid complex	
El Dib et al., 2014 [15]	5-year-old boy		*Coccidioidomycosis*	Patient died before receiving required antifungal therapy	Died
Cavalcante et al., 2014 [16]	10-year-old girl	Juvenile systemic lupus erythematosus (JSLE)	*Cryptococcus neoformans*	Liposomal amphotericin B (3 mg/kg)	Died
França et al., 2012 [17]	14-year-old girl	Juvenile systemic lupus erythematosus (JSLE)	*Histoplasma capsulatum*	Liposomal amphotericin B (1 mg/kg)	Died
Pereira et al., 2004 [18]	2-year-old girl	Lymphoproliferative syndrome	*Paracoccidioides brasiliensis*	Intravenous sulfamethoxazole-trimethoprim (10 mg/kg trimethoprim)	Died
Hsu et al., 1998 [19]	23-month-old boy	Acute myeloid leukemia (AML)	*Trichosporon beigelii*	Amphotericin B	Died
Wee et al., 2019 [20]	13-year-old boy	Acute lymphoblastic leukemia (ALL)	*Saprochaete clavata*	Amphotericin B and voriconazole (10 weeks)	Alive
Trabelsi et al., 2015	17-year-old boy	AML	*Saprochaete clavata*	AMB (60 mg/d)	Died

[21]					
Parahym et al., 2015 [22]	15-year-old boy	AML	*Saprochaete capitata*	Caspofungin; amphotericin B lipid complex (5 mg/kg) (24 days), and voriconazole (400 mg/d)	Alive
Trabelsi et al., 2015 [21]	17-year-old boy	AML	*Saprochaete capitata*	AMB (60 mg/d)	Died

Table II. Literature data on septic shock in adults with invasive fungal disease

Source	**Age**	**Primary disease**	**Etiology**	**Treatment**	**Outcome**
Caldas et al., 2022 [23]	43-year-old woman	Crohn's Disease on treatment with infliximab and azathioprine	*Saprochaete clavata*, *Legionella pneumophila serogroup 1*	Liposomal amphotericin B (L-AMB)	Died
Duarte et al., 2021 [24]	66-year-old woman	Acute myeloid leukemia (AML)	*Saprochaete capitata*	L-AMB and flucytosine	Died
Lo Cascio et al., 2020 [25]	20-year-old woman	Acute lymphoblastic leukemia (ALL)	*Saprochaete clavata*	Caspofungin	Died
Buchta et al., 2019 [26]	Patient 1 — 45-year-old man Patient 2 — 61-	1 — AML after allo-HCT 2 — AML 3 — AML after allo-HCT 4 — AML after	1 — *Saprochaete clavata* 2 — *Saprochaete clavata*	1 — amphotericin B (1 mg/kg) 2 — amphotericin B (1 mg/kg), lipid-based AMB (5 mg/kg)	1 — died 2 — survived (but died from early relapse of AML later) 3 — died

	year-old woman Patient 3 — 58-year-old woman Patient 4 — 50-year-old woman Patient 5 — 66-year-old woman	auto-HCT 5 — DLBCL	3 — *Saprochaete clavata* 4 — *Saprochaete clavate* (*+Candida albicans were cultivated from nasopharyngeal swab*) 5 — *Saprochaete clavata* *+ Candida glabrata*	3 — amphotericin B (0.7–1 mg/kg) lipid-based AMB (5 mg/kg), voriconazole (2 × 200 mg) 4 — amphotericin B (0.7–1 mg/kg) 5 — micafungin (100 mg), voriconazole (2 × 200 mg)	4 — died 5 — died
Ben Neji et al., 2019 [27]	39-year-old man	AML	*Saprochaete capitata*	Deoxycholate amphotericin B	Died
Alobaid et al., 2019 [28]	67-year-old woman	Diabetes, hypertension, ischemic heart disease, left ventricular failure, peripheral vascular disease, bronchial asthma and obstructive sleep apnea	*Saprochaete capitata*	No antifungal therapy	Died
Bansal et al., 2018	29-year-old	AML	*Saprochaete capitata*	L-AMB	Died

[29]	woman				
Hajar et al., 2018 [30]	82-year-old man	Kidney transplant recipient	*Saprochaete capitata*	L-AMB	Died
Pamidimukkala et al., 2017 [31]	48-year-old woman	Biphenotypic acute leukemia	*Saprochaete capitata concomitant Enterococcus gallinarum*	AMB emulsion 5 mg/kg	Died
Fernández-Ruiz et al., 2017 [32]	55-year-old man	Refractory acute leukemia	*Saprochaete capitata*	Amphotericin B and voriconazole	Died
Del Principe et al., 2016 [33]	50-year-old woman	Mantle cell lymphoma	*Saprochaete clavate* On day 19, *Saprochaete clavata* was isolated from blood with serum BG level being >500 pg/mL	L-AMB (3 mg/kg), 47 days	Died on day 60 from chemotherapy initiation because of lymphoma progression
Subramanya Supram et al., 2016 [34]	Patient 1 — 77-year-old woman Patient 2 — 80-year-old man	Patient 1 — hypertension, Alzheimer's disease Patient 2 — COPD, hypertension	Patient 1 — *Saprochae capitata* + *Flavobacter spp.* (endotracheal aspirate) Patient 2 — *Saprochaete capitata*	Patient 1 — no antifungal therapy Patient 2 — fluconazole (400 mg/day for 4 days)	Patient 1 — died Patient 2 — died

Trabelsi et al., 2015 [21]	Patient 1 — 25-year-old woman Patient 2 — 57-year-old man	AML	*Saprochete capitata*	Patient 1 — AMB (60 mg/d) Patient 2 — AMB (80 mg/d) + voriconazole (2 × 200 mg)	Patient 1 — died Patient 2 — died
Picard et al., 2014 [35]	Patient 1 — 46-year-old woman Patient 2 — 70-year-old man Patient 3 — 63-year-old woman	AML	*Saprochaete clavata*	Patient 1 — L-AMB and voriconazole Patient 2 — caspofungin Patient 3 — L-AMB and voriconazole	Patient 1 — survived septic shock, died because of hemorrhage Patient 2 — died Patient 3 — died
García-Ruiz et al., 2013 [36]	55-year-old man	ALL	*Saprochaete capitata*	L-AMB (4 mg/kg/d) + voriconazole	Died
Saghrouni et al., 2012 [37]	47-year-old man	AML	*Saprochaete capitata*	Amphotericin B_ (1 mg/kg) for 14 days; then 2 voriconazole 2 × 200 mg	Died
Avelar Rodriguez et al., 2017 [38]	28-year-old man	Cocaine abuse and Child-Pugh class C alcoholic liver cirrhosis	Rhinocerebral mucormycosis, *Candida glabrata*	L-AMB 3 mg/kg	Died

Fernández-Ruiz et al., 2017 [32]	56-year-old man	Solid cancer, abdominal surgery, prolonged ICU stay	*Wickerhamomyces anomalus*	AMB (9 d), then fluconazole (5 d)	Alive
Taniguchi Y et al., 2009 [39]	18-year-old man	Mitochondrial encephalomyopathy accompanied by refractory anemia and chronic renal failure	*Lecythophora mutabilis*	Micafungin 5 mg/kg, L-AMB (3 mg/kg)	Died
Hennequin et al., 2000 [40]	47-year-oldman	Adenocarcinoma of lower esophagus	*Saccharomyces boulardii*	Fluconazole (100 mg/d) initiated on day 35 for six weeks	Alive

allo-HCT — allogeneic hematopoietic cell transplantatin; auto-HCT — autologous hematopoietic cell transplantatin; COPD — chronic obstructive pulmonary disease; DLBCL — diffuse large B-cell lymphoma; ICU — intensive care unit

Discussion

Invasive fungal infections represent a serious medical problem worldwide and are a major cause of morbidity and mortality in patients with hematological malignancies. Other immunocompromised patients are also at high risk of IFD mainly because of the increased use of immunosuppressive and cytotoxic therapies, as well as improved diagnostic techniques. *Candida* and *Aspergillus spp*. are major causative agents.

However, with the new prevention strategies, new species are increasingly being reported as being agents of bloodstream infections (BSI) or disseminated fungal disease. Obviously, a frequent presentation of *Candida spp.* is a bloodstream infection with typical clinical symptoms. However, such a presentation is rare in patients with another fungal etiology. Septic shock is the most dangerous presentation of infection, bringing the risk of poor prognosis. In this paper, we have

searched for patients with non-*Candida* invasive fungal infection presenting as septic shock. We have found a limited number of reports, both in children and adults.

Septic shock is always a medical emergency. It requires the immediate administration of antimicrobials. Usually, bacterial etiology is suspected and adequate empirical treatment broadly covering the most probable pathogens is promptly started. In immunocompromised patients, in the presence of severe infection with symptoms of septic shock, atypical agents including fungal etiology should also be considered. One should be aware also of mixed etiology of septic shock in patients.

The most striking finding of our analysis is the low survival of patients, as only 26.1% of children and 17.9% of adults survived fungal infection with septic shock. Even with the long time period of inclusion, this survival rate was low in comparison with the outcome of IFD seen in leukemic patients both in the first [3, 41] and second [42, 43] decades of this century.

Immunocompromised patients, especially those with hematological malignancy who develop septic shock caused by fungal infection, are at very high risk of mortality. There are two options to improve therapeutic effect. Firstly, starting the empirical antifungal therapy as soon as possible is essential to increase the chance of survival in these patients. Secondly, it is recommended that early source control, including catheter removal, is a key factor influencing the outcome of leukemic or transplant patients with septic shock or sepsis of fungal etiology [4, 8].

The limitation of this study was the heterogenous population in terms of primary diagnosis, primary treatment, and etiology of fungal infection. We also limited the analysis to non-*Candida* etiology, because the symptoms of sepsis are relatively more frequent in *Candida* bloodstream infection.

Conclusion

Septic shock is a very rare presentation of fungal infection in immunocompromised patients, but the mortality is very high both in children and adults.

Authors' contributions

KC, JS — design of study. RD, MRP, KC — provision of clinical data. All authors — analysis of clinical data. TS, JS — literature search and analysis of data. TS, JS — writing manuscript. All authors — critical revision and final approval.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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