Candida-Related Immune Response Inflammatory Syndrome Treated with Adjuvant Corticosteroids and Review of the Pediatric Literature

Adjuvan Kortikosteroid ile Tedavi Edilen *Candida*-İlişkili İmmün Yanıt Enflamatuvar Sendromu ve Pediatrik Literatür Derlemesi

Dildar Bahar Genç[1], Sema Vural[1], Nafiye Urgancı[2], Tuğçe Kurtaraner[3], Nazan Dalgıç[4]

[1]*Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatric Oncology, İstanbul, Turkey*

[2]*Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatric Gastroenterology, İstanbul, Turkey*

[3]*Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatrics, İstanbul, Turkey*

[4]*Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatric Infectious Disease, İstanbul, Turkey*

To the Editor,

Chronic disseminated candidiasis (CDC) is a potentially fatal complication observed in febrile neutropenia [1]. The diagnosis is usually made after neutrophil recovery and microbiological proof has been often negative [2]. Granulomatous histopathology, radiological lesions coincident with resolution of granulocytopenia, and rapid response to corticosteroids favors immune-mediated pathogenesis. Recently, CDC has been suggested to be related to Immune response inflammatory syndrome (IRIS), an exacerbated response to a preexisting antigenic stimulus in patients with rapid immune restoration [1,3]. IRIS has been mostly documented in HIV-infected patients with immune recovery after antiretroviral therapy [4]. Here, we present a case of *Candida*-related IRIS and review the current literature on children.

A male, aged 6 years and 7 months, with B-cell acute lymphoblastic leukemia was treated for presumed typhlitis with meropenem, teicoplanin, and amphotericin B during induction therapy. Thoracoabdominal CT scans revealed hepatosteatosis/hepatomegaly. Fever subsided on the 2nd day. During steroid tapering and on the 8th day of antibiotics, the patient developed fever and abdominal pain with marked elevation of liver enzymes, predominantly of GGT. Bone marrow examination showed no evidence of blasts or hemophagocytosis and the blood count was normal. Control imaging showed typical widespread hepatic bull's eye lesions (Figure 1). The liver biopsy demonstrated granulomatous inflammation, but no fungus was detectable. According to European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria, the diagnosis was possible invasive fungal infection, most likely candidiasis. Reappearance of symptoms after neutrophil recovery indicated IRIS. We empirically administered dexamethasone for 14 days. Fever disappeared after 24 h and liver function tests improved in 1 week. He was discharged with oral voriconazole. During vincristine therapy, voriconazole was replaced with amphotericin B to avoid toxicity. In the 13th month of voriconazole, the liver lesions showed partial regression and calcification. As re-biopsy was negative for microorganisms and showed only rare microgranulomas, we stopped the voriconazole. The patient completed chemotherapy and has been without any exacerbation for 32 months since the initial diagnosis of IRIS.

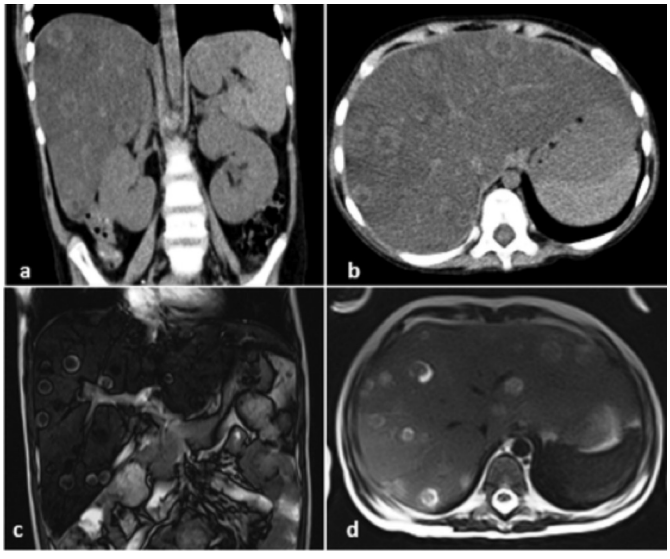

Figure 1. Coronal and axial computed tomography images (a, b); coronal and axial magnetic resonance images of circumscribed typical hepatic *Candida* lesions (c, d).

Clinical and/or radiological deterioration after neutrophil recovery is a well-known entity in patients treated for opportunistic infections [4]. The immune system shifts towards Th-1 type response and amplifies proinflammatory cascades [1]. Therefore, the severity of radiological/clinical findings might depend on the immune status of the patient [5,6]. IRIS is a diagnosis of exclusion; other possible causes of persistent fever should be evaluated. If the clinical scenario is not consistent with preexisting disease, treatment side effects, or a possible newly acquired pathogen, IRIS deserves diagnostic consideration. In the previous *Candida*-related IRIS reports on children with cancer, all patients had fever and liver dysfunction accompanying normal neutrophil counts. Liver biopsies showed granuloma formation. Tissue cultures for fungi were negative in all samples except one. The

Table 1. Review of pediatric cases of *Candida*-related Immune response inflammatory syndrome treated with corticosteroids.

Authors	Age (years)	Diagnosis	Proof of *Candida*	ANC/mm^3	Biopsy	Liver Dysfunction	Antifungal Treatment	Steroid Dose and Duration	Outcome
Saint-Faust et al. [11]	12	AML	*Candida* antigen and serology (+)	2800	Granulomatous lesion, *Candida* (-)	(+)	AmB (1 mg/kg)	Pred 1 mg/kg, 60 days	Radiological improvement in 30 days. At 24 h, fever and pain disappeared and liver dysfunction improved.
Saint-Faust et al. [11]	8	ALL	*Candida* serology (+)	2580	Granulomatous lesion, *Candida* (-)	(+)	L-AmB (3 mg/kg)	Pred 1 mg/kg, 90 days	Fever and pain disappeared in 2 days. radiological improvement in 30 days.
De Castro et al. [10]	Median: 46 (2-76)	14 mixed	*	Unknown	Unknown	Mostly (+)	*	Mean: 1 mg/kg/day* Median: 1.5 (1-10 months)	*
Conter et al. [8]	17	Lymphoma	*Candida* serology (+)	12,000	Granulomatous lesion, pseudomycelia (+)	(+)	AmB (1 mg/kg)	Pred 1 mg/kg, 120 days	Fever disappeared in 24 h, clinical improvement in 7 days, radiological improvement in 6 weeks.
Legrand et al. [3]	Median: 18.6 (2-65)	10 hematological malignancies	Blood culture (+), 1/10; stool culture (+), 7/10; urine culture (+), 1/10	Median: 19,372	Yeast positive in smear (5/10), culture positive (1/10), granulomas	(+)	*	Median** 0.66 mg/kg/day (0.4-2) Median 109 (49-240 days)	Clinical improvement at median 4.5 days (1-30). Radiological improvement in 107 days (mean: 30-210 days).
Bayram et al. [7]	16 months	ALL	(-)	WBC: 36,100	(-)	(+)	Fluconazole, voriconazole	DXM 0.5 mg/kg, 14 days	Fever disappeared in 3 days, liver tests normalized in 7 days, USG findings normalized in 30 days.
Current case	6.5	ALL	(-)	2750	Granulomatous lesion, *Candida* (-)	(+)	L-AmB (3 mg/kg), then voriconazole	DXM 0.4 mg/kg, 14 days	Fever disappeared in 24 h, liver function tests improved in 1 week. Radiological improvement in 2 months.

*Case series studies, i.e. details unspecified. ALL: Acute lymphoblastic leukemia, ANC: absolute neutrophil count, AmB: amphotericin B, L-AmB: liposomal amphotericin B, Pred: prednisolone, DXM: dexamethasone, **: prednisone equivalent.

most commonly administered antifungal agent was amphotericin B. Details of steroid therapy and the outcomes are presented in Table 1 [3,7,8,9,10,11]. Increased susceptibility to infection might be a drawback for prolonged corticotherapy. However, neither *Candida* reactivation nor other new opportunistic infections have been reported [3].

Candida-related IRIS has been rarely reported in children. Early recognition and appropriate management of IRIS might prevent unnecessary diagnostic procedures, antibiotic usage, and chemotherapy delays.

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Keywords: Leukemia, Febrile neutropenia, *Candida*, Immune response inflammatory syndrome

Anahtar Sözcükler: Lösemi, Febril nötropeni, *Candida*, İmmün yanıt enflamatuvar sendromu

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Address for Correspondence/Yazışma Adresi: Dildar Bahar GENÇ, M.D.,
Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatric Oncology, İstanbul, Turkey
Phone: +90 212 373 66 57
E-mail : baharbeker@yahoo.com

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Posttranslational Modifications of Red Blood Cell Ghost Proteins as "Signatures" for Distinguishing between Low- and High-Risk Myelodysplastic Syndrome Patients

Düşük ve Yüksek Risk Miyelodisplastik Sendrom Hastalarını Ayıran "İşaretler" Olarak Kırmızı Kan Hücre Zarı Proteinlerinin Posttranslasyonel Modifikasyonları

Klara Pecankova, Pavel Majek, Jaroslav Cermak, Jan E. Dyr
Institute of Hematology and Blood Transfusion, Prague, Czech Republic

To the Editor,

Myelodysplastic syndrome (MDS) comprises a heterogenic group of oncohematological diseases that affect hematopoiesis. Although the precise cause of MDS is unknown, multiple factors are involved, one of the most widely implicated of which is oxidative stress. However, it is unclear whether oxidative stress is a cause of MDS or an effect of other pathological mechanisms.

Red blood cells (RBCs) are the first cells exposed to stress stimuli. They are highly vulnerable to free radical accumulation, which leads to the oxidative stress that induces damage in proteins and