SERUM IMMUNOGLOBULIN VALUES AND THE DEVELOPMENT OF INVASIVE FUNGAL INFECTIONS IN THE HEMATOLOGICAL PATIENTS

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ABSTRACT

Purpose*: The aim of this study was to investigate whether lower serum immunoglobulins, especially IgG, increase the development of fungal infection in patients with hematological malignancy.*

Material and methods*: Patients, who were hospitalized due to hematological maligancies at Ministry of Health Istanbul Training and Research Hospital, between April 2015 and January 2017, in hematology and internal medicine clinics and diagnosed with a fungal infection in compatible with a galactomannan positivity as well as frosted glass opacities and nodular infiltrates on high resolution computed tomography (HRCT) and chest X-ray, with or without a yielded microbiological culture, were evaluated in this retrospective case - control study.*

Results*: A total of 22 patients with hematological malignancies (HM) and invasive fungal infections (IFI; cases group) were compared with 22 patients with HM without IFI (control group) in the study. The IgG level in the cases group was significantly lower than the control group (p: 0.044). The mean IgA and M values in the cases group and control group did not differ significantly ($p > 0.05$). The mean Galactomannan value in the cases group was significantly higher than the control group ($p < 0.041$).*

Conclusion*: Serum IgG levels were found to be lower in patients with invasive fungal infection during the treatment of hematologic malignancy than in patients with hematological malignancy and without invasive fungal infection. There needs a randomized-control study to describe the relationship between low serum immunglobulin values in patients with hematological malignancy and development of invasive fungal infection.*

Keywords*: Immunglobulins, fungal infections, immunoglobulin G, galactomannan, HRCT.*

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Introduction

Developments in antimicrobial treatment strategies have led to invasive fungal infections becoming the leading causes of morbidity and mortality in cancer patients[(1)]. This is related to the spontaneous or iatrogenic (catheter, etc.) degradation of skin integrity and mucosal barrier, as well as the dysfunction of natural and adaptive immune system components by the hematological disease, the antineoplastic or immunosuppressive therapy.

The highest incidence of fungal infection in cases with acute leukemia has been reported to belong to filamentous fungal infections (especially Aspergillus species, less frequently Zygomycetes)[(2)]. In addition, when invasive candida infections were diagnosed in cancer patients, a venous catheter, almost all of these patients had a venous catheter, aggressive chemotherapies, a broad spectrum antibiotic use in the last two weeks and corticosteroid use were found in more half of the cases[(3)].

If immunity is impaired by hematological malignancies and deep cytopenia is caused by cancer chemotherapy, or the loss of function occurs, fungal infections can cause life-threatening serious consequences. At this point, the determination of conditions that predispose to fungal infections, which diagnosis and managemet are more difficult than bacterial agents, and early detection and management of prophylactic and early antifungal treatment will contribute to cost-effectiveness and reducing the mortality rates. Galactomannan, which is used as a test to diagnose invasive Aspergillus infection earlier, is a cell wall component of Aspergillus and released during reproduction. It was used for the diagnosis of invasive aspergillosis by many researchers[4].

The aim of this study was to investigate whether lower serum immunoglobulins, especially IgG, increase the development of fungal infection in patients with hematological malignancy.

Materials and methods

Patients, who were hospitalized due to hematological maligancies at Ministry of Health Istanbul Training and Research Hospital, between April 2015 and January 2017, in hematology and internal medicine clinics and diagnosed with a fungal infection in compatible with a galactomannan positivity as well as frosted glass opacities and nodular infiltrates on high resolution computed tomography (HRCT) and chest X-ray, with or without a yielded microbiological culture, were evaluated in this retrospective case - control study. White blood cell (WBC), neutrophil, lymphocyte counts, serum galactomannan values, serum immunoglobulin (IgG, IgA, IgM) values were evaluated. Patients, who had an evidence of bacterial and/or viral infection (bacterial growth in the cultures taken, clinical response to antibacterial antibiotics in 72 hours, clinical response to symptomatic treatment) were not included in the study.

The approval was obtained from the local ethics committee of Istanbul Education and Research Hospital (file number: 893 and date: 09/12/2016) for the study. The data of the patients were provided by the hospital database system. The values of patients were compared with those of a control group which coprised of patients who had a hematological malignacy, but were not diagnosed with a fungal infection and not treated during the follow-up at the clinic. Complete blood count parameters (WBC, Neutrophil, Lymphocyte) were analysed with the automated system. Serum immunoglobulins (IgG, IgA and IgM) levels were determined by a commercial nephelometry assay using a BN-II device (Dade Behring, Marburg, Germany). The manufacturer indicates the following reference intervals for healthy adults: IgA 70-400mg/dl, IgG 700-1600mg/dl and IgM 40-230mg/dl. Aspergillus galactomannan antigen testing was performed using the Platelia Aspergillus EIA commercial enzyme immunoassay kit (Bio-Rad Laboratories, Marnes-la-Coquette, France). Blood samples of patients were analyzed twice weekly and the results computed as an index in which values of ≥0.5 relative to the optical density of the control sample measured with a semiautomatic analyzer (Behring ELISA processor III; Dade Behring, Marburg, Germany) were considered positive samples.

Statistical Analysis

SPSS 22.0 program was used for statistical analysis. Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of the variables was analysed by the Kolmogorov Smirnov test. Independent sample t and Mann-Whitney U tests were used in the analysis of quantitative independent variables. Fischer' s exact test was used to analyse the qualitative independent variables. The level of influence was investigated by univariate and multivariate logistic regression analysis. Statistical significance level of alpha (p) was considered as < 0.05.

Results

A total of 22 patients with hematological malignancies (HM) and invasive fungal infections (IFI; cases group) were compared with 22 patients with HM without IFI (control group) in the study (Table 1). The number of male patients in the patients with IFI group was significantly higher than the control group (p: 0.03). The mean WBC, neutrophil, and lymphocyte counts were found similar in both groups ($p > 0.05$). The IgG level in the cases group was significantly lower than the control group (p: 0.044). The mean IgA and M values in the cases group and control group did not differ significantly ($p > 0.05$). The mean Galactomannan value in the cases group was significantly higher than the control group ($p < 0.041$).

	Patients with invasive fungal infection (n: 22)	Patients without invasive fungal infection (n: 22)	*p*
Age			
Mean ± SD	49.2± 17.5 years	47.65±18.51 years	
Range	19-75 years	20-73 years	0.528
Median	51 years	46 years	
Gender			
Female	5	12	**0.03**
Male	17	10	
Body mass index	25.2± 3.9	25.3± 3.5	
18-24	9	12	0.890
25-29	11	7	
≥ 30	2	3	
Hematological malignancy			
T-cell lymphoma	1	-	
Acute lymphoblastic leukemia	4	5	
Acute myeloblastic leukemia	11	10	
Burkitt lymphoma	1	1	
Diffuse large cell lymphoma	1	1	
Hairy cell leukemia	1	1	0.892
Hodgkin lymphoma	1	1	
Chronic lymphocytic leukemia	-	1	
Multiple myeloma	2	1	
Central nervous system lymphoma	1	-	
Lymphocyte count (x 10^3)	4.05± 12.47	1.12± 1.67	
Median	0.74	0.7	
< 1000	14	14	0.725
1000-3500	6	7	
> 3500	2	1	
Ig G (x 10^3)	1.12 ± 0.53	1.68 ± 1.23	
Median	0.95	1.53	
< 700	3	2	**0.044**
700-1600	15	11	
> 1600	4	9	
Galactomannan	1.2 ± 2.2	0.1 ± 0.1	
< 0.5	14	22	**0.041 0.002**
> 0.5	8	0	
Findings with thorax high-resolution computed tomography			
Normal	1	20	
Nodular	9	1	**0.0005**
Ground glass	9	1	
Acino nodular + ground glass	3	0	

Table 1: The demographic data and findings of patients with invasive fungal infection and Patients without invasive fungal infection.

The rate of patients with Galactomannan value > 0.5 in the cases group was significantly higher than the control group (p: 0.02). The findings with thorax computed tomography were more common seen in the cases group than the control group (p: 0.0005).

There was no significant difference in age, BMI, WBC, neutrophil, lymphocyte, IgG, IgA, IgM values between the case and control groups in the univariate model (p > 0.05), but there was a significant difference in terms of sex (0.03), galactomannan value (p: 0.02) and findings with thorax computed tomography (0.0005). In the multivariate reduced model, the positive galactomannan value and findings with high resolution computed tomography (HRCT) were observed as indepented risk factors for the presence of an invasive fungal infection.

Discussion

Humoral and cellular immunity defects due to different immunochemotherapeutic agents form the basis for the infections, especially mortal invasive fungal infections. Prior to the 1990s, it was thought that antibody-mediated immune response did not involve in host defense against fungal infections[5]. This has been altered when Dromer and colleagues demonstrated the protective effect of the monoclonal antibody against lethal *C. neoformans* infection in rats[6]. Gigliotti and Hughes reported also that the monoclonal antibody is protective against *P. jirovecii* infection, as hypogammaglobulinemia related disseminated cryptococcal infection was presented[7, 8].

In our study, low Ig value was related to invasive fungal infection in similar to those studies. Patients with hematological malignancy and hipoglobilinemia should be followed up with galactomannan and computed tomography imaging to diagnose IFI earlier. It is known that IgG is the strongest opsonin, which is the highest amount of antibody in the plasma. Thus, low IgG leads to decreased opsonization and consequently decreased phagocytosis and antibody-dependent cellular cytotoxicity[9]. As a result, it may be particularly contributing to the development of invasive fungal infection. we could not carry out the IgG subgroups because of the limited facilities. Plasma IgA accounts for 15% of all immunoglobulins. Van Spriel et al. have shown that increased Ig A levels protect against *C. albicans* in rats[10].

In our study, there was no significant difference in IgA levels between the cases group and the control group. Similarly, Subramaniam et al. revealed in another study that low IgM levels make susceptible to *C. neoformans* infection[26]. In our study, no significant difference was found between IgM levels of cases and control groups. Insignificant findings in IgM levels, such as in IgA levels, may be due to low patient numbers. On the other hand, only a significant difference in IgG compared to other antibody types.

The important findings in our study were a positive correlation between a lower IgG level and higher serum galactomannan levels with the findings by CT of thorax.

In a study by Bergeron and his colleagues, Aspergillus colonization was reported to be more common in non-acute leukemia (AL) patients than in AL patients and in patients with leukocyte counts more than 100/mm^3[11]. In our study, there was no significant difference between the WBC values of the cases and control groups. In a study with HIV-infected patients, Coelho et al. reported that high lymphocyte counts are protective effect against opportunistic infections, such as esophageal candidiasis and *P. jerovecii* pneumonia[12].

Peng et al. reported that decreased Th17 levels in allogeneic hematopoietic stem cell transplant recipients during the immunization period were associated with an increased incidence of invasive fungal infection[13]. Cumbo and Segal reported that the severity and duration of neutropenia affect the prognosis of invasive fungal infections[14]. In another study of Shahbudak and colleagues reported that prolonged and deep neutropenia in the induction phase of chemotherapy in a pediatric patient group with ALL was the major cause of invasive fungal infection development[15]. In our study, there was no significant difference in neutrophil and lymphocyte values between both groups. An effective prophylaxis, improvement of environmental conditions, other immunological factors of the patients and different numbers of patients in the studies were likely to cause different outcomes in our study and other studies.

Galactomannan is an useful test to diagnose invasive Aspergillus infection earlier in patients with hematological malignancy. Yu et al. reported that the best sensitivity and specificity were achieved at 0.5 pg/ L cut-off value for the galactomannans[16].

In this study, the sensitivity of galactomannan was 54.5% followed by the specificity with 77.9%; the positive predictive value with 20.%7; and the negative predictive value with 94.2%. The mean galactomannan value was significantly higher in the cases group than the control group.

Invasive fungal infections often occurs in the upper and lower airways of immunocompromised patients with hematologic malignancy. HRCT is often used to identify these lesions[17]. Althoff and colleagues repoted that the most common finding was nodule formation (84% of patients with aspergillosis, 95% of patients with candidiasis) by HRCT, as nodular, asino-nodular, and ground glass lesions were common by HRCT in the diagnosis of pulmonary fungal infection of our cases[17].

Although the gold standard for invasive fungal infections is still an invasive histopathological diagnosis, invasive diagnostic methods are not widely used. Galactomannan and HRCT are main two diagnostic procedures to diagnose invasive aspergillus infection, as (1→3)-β-D-glucan (BG) and blood culture are more valuable procedures for the Candida infections. Patients who have lower Ig G value should be concerned for the development of an invasive fungal infection and in case of suspicion, HRCT and galactomannan measurement twice in a week should be performed and anti-fungal prophylaxis should be administered to high- risk patients[18-21].

These limitations of our study includes the existence of small study populations in the cases and control groups, a retrospective case-control study that was carried out, immunglobulin values that could not be measured at the diagnosis of hematological malignancy, during chemotherapy, at the diagnosis of IFI, after recovery of IFI, existence of half of the patients in both groups with acute myeloblastic leukemia that IFIs, especially invasive aspergillus infections, are frequent, and absence of histopathological diagnosis IFI. The results of the study will be more clear if immunglobulin values are measured in patients with haematological malignancies are performed as a prospective randomized controlled study on a large number of patients with specific subtypes.

As a result, (koma) IgG levels were found to be lower in patients with invasive fungal infection during the treatment of hematologic malignancy than in patients with hematological malignancy and without invasive fungal infection.

Patients who have lower Ig G value should be concerned for the development of an invasive fungal infection, and HRCT and galactomannan measurement twice in a week should be performed and anti-fungal prophylaxis should be administered to high- risk patients. There needs a randomized-control study to describe the relationship between low serum immunglobulin values in patients with hematological malignancy and the development of invasive fungal infection.

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