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Original Article

Invasive Pulmonary Aspergillosis in Patients with Haematological Malignancies and Hematopoietic Stem Cell Transplantation: a Single-Center Study

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Abstract

Aim: The aim of this study was to evaluate the clinical significance of *Aspergillus* Galactomannan antigen (GM) test for the diagnosis of invasive pulmonary aspergillosis (IPA) in patient with hematological malignancies, including patients undergoing hematopoietic stem cell transplantation (HSCT).

Materials and methods: Between January 2016 and June 2019, ninety patients were tested for GM. A total of 134 blood and 19 bronchoalveolar lavage (BAL) samples were analyzed using Platelia *Aspergillus* Ag Enzyme-Immuno Assay (Bio-Rad Laboratories). The median age of patients was 63 years (range 25–81). Fifty-six patients (62.2%) were male. All patients were allocated into five groups on the basis of their GM results.

Results: A positive GM antigen test was detected in 16 patients (17.7%). Of these, ten had positive serum samples (group I). After re-testing, 1 patient from group I gave a negative result. Five patients with negative serum samples gave positive BAL results (group II). One patient had positive both serum and BAL samples (group III). Fifteen GM positive patients (9 from group I, group II, and III) were categorized as probable IPA. Thirty-six patients (40%) negative for GM (group IV) were considered with a possible IPA. IPA was excluded in 38 patients (42.2%) (group V). Anti-mould therapy was initiated in all 15 patients who were considered to be cases with probable IPA. IPA was the immediate cause of death in 3 cases (25%).

Conclusions: Our results demonstrated the clinical applicability of the GM test for screening of IPA in high-risk patients with hematological malignancies and HSCT.

Keywords

ELISA, galactomannan, mold infection, oncohematology, stem-cell transplantation

INTRODUCTION

Patients with hematological malignancies and those with hematopoietic stem cell transplantation (HSCT) are at high risk of developing severe, life-threatening infections with mortality rates as high as 55%.[1]

Invasive pulmonary aspergillosis (IPA) is one of the most important infectious complications with frequency of 12% in individuals with hematological malignancies and between 2% and 8% after autologous and allogeneic stem-cell transplantation. Depending on the underlying disease, the IPA-associated mortality may reach as high as 88%.[2]

The aspergillosis is an exogenous mycotic infection caused by the widespread fungi belonging to the genus *Aspergillus* with *A. fumigatus, A. flavus, A. niger*, and *A. terreus* being the most clinically important species.[3] The infections associated with *Aspergillus* spp. can vary from local skin infections to severe infections with high mortality such as IPA.[4,5] Very rarely, these moulds can cause invasive diseases in immunocompetent individuals.[3,6]

The major risk factors for IPA are prolonged neutropenia (<500 cells/μl for more than 10 days), hematological malignancies, chemotherapy, HSCT, a continuous (>3 weeks) and high-dose corticosteroid therapy, and advanced stages of AIDS.[5]

Detection of *Aspergillus* galactomannan antigen (GM) and beta-D-glucan by immuno-enzyme assays and molecular genetic methods such as polymerase chain reaction (PCR) are currently used to diagnose IPA.[7] All three methods possess high specificity and sensitivity. The GM antigen test, relatively inexpensive and fast, is specifically adjusted for the diagnosis of IPA.[8]

AIM

The aim of this study was to evaluate retrospectively the clinical significance of *Aspergillus* GM test for the diagnosis of IPA in patients with hematological malignancies, including patients after HSCT.

MATERIALS AND METHODS

A total of 90 patients with hematological malignancies or HSCT, treated in the Hematology Clinic of St Marina University Hospital, Varna between January 2016 and June 2019 were included in this study. The inclusion criteria were: febrile neutropenia defined as episodes of fever >38°C and an absolute neutrophil count (ANC) $<1\times10^9$/l or a continuous (>3 weeks) and high-dose (>60 mg/kg) corticosteroid therapy even without neutropenia or imaging results suspicious for IPA (halo-sign, crescent sign, tree in bud, cavitated lesion or consolidation) and unresponsiveness to the standard antibacterial therapy. The cases were evaluated and categorized according to the revised and updated EORTC/MSG criteria as proven, probable, possible[9] or no IPA. Patients fulfilling only the host criteria were classified with no IPA. None of the included patients received antifungal prophylaxis during the study.

The Platelia *Aspergillus* Ag Enzyme-Immuno Assay (Bio-Rad Laboratories) was used to quantify GM indices in serum samples (n=134) and BAL fluid samples (n=19) according to the manufacturer's instructions. Test results with the following optical densities (OD) were considered positive: single serum/plasma ≥1.0, BAL fluid ≥1.0 or single serum/plasma ≥0.7 and BAL fluid ≥0.8.[9] All clinical samples collected from the patients were sent to the microbiology laboratory where they were tested immediately. The patients undergoing bronchoscopy signed an informed consent before the procedure.

All BAL samples were inoculated on Sabouroux agar, blood, chocolate and MacConkey agar and were cultivated for 72 hours at 30°C.

RESULTS

Following the inclusion criteria, a total of ninety patients (median age of 63 years (ranging from 25 to 81 years), and male/female ratio of 1.6:1 were tested for GM during the three-year study period. Sixty-seven patients (74.4%) received intensive chemotherapy for different hematological malignancies and 23 (25.6%) patients underwent HSCT. A therapy with piperacillin/tazobactam was initiated in 36 patients before testing for GM and 54 patients received fluoroquinolone or trimethoprim/sulfamethoxazole.

A comparative characterization of the patients included in this study presented as IPA and non-IPA group is shown in **Table 1**.

A total of 134 serum samples and 19 BAL fluid samples were collected from all 90 patients enrolled in this study. On the base of their GM results, the patients were distributed into five groups **(Table 2)**.

Sixteen patients (17.7%) had a positive GM antigen test **(Table 2)**. Of these, 10 had positive serum samples (OD index varying from 1.0 to 6.09) and were included in group I. In 5 of these patients, BAL fluid specimen was collected in parallel, but remained negative (OD index <0.5). After re-testing, one patient from group I tested negative and was interpreted as false-positive.

Five patients with negative serum samples (OD index <0.5), gave a positive BAL score with the OD index varying from 1.0 to 4.60 - group II **(Table 2)**. Only one patient had positive both serum (OD index 1.06) and BAL samples (OD index 0.8) - group III.

Fifteen GM positive patients (9 from group I and all from group II and III) were categorized as probable IPA on the base of host factors, clinical features and mycological evidence. Two of these patients (one with NHL and one with ALL) were allogeneic stem cells transplant recipients.

Patients that gave negative GM test results (36 serum and 8 BAL tests; OD index <0.5) but met host criteria and

Table 1. A comparative characterization of patients included in the study presented as IPA and non-IPA group

Characteristics	IPA group* (n=15)	non-IPA group (n=75)
Age	42–80	25–81
Sex		
Male (n)	n=10	n=46
Female (n)	n=5	n=29
Disease		
Acute myeloid leukemia (AML)	n=5	n=34
Acute lymphoid leukemia (ALL)	n=4	n=9
Hodgkin's disease (HD)	n=2	n=2
Non-Hodgkin's lymphoma (NHL)	n=2	n=15
Aplastic anemia (AA)	n=1	n=3
Myelodysplastic syndrome (MDS)	n=1	n=1
Multiple myeloma (MM)		n=5
Chronic lymphoid leukemia (CLL)		n=4
Chronic myeloid leukemia (CML)		n=2
WBC at diagnosis	$0.00–2.99\times10^9$/l	$0.35–7.29\times10^9$/l
Median time of neutropenia	9 days	4 days

*includes only patients with probable IPA

Table 2. Results from *Aspergillus* Galactomannan Ag test

Patients (n)	Tested serum samples for GM (n) and results	Tested BAL fluid samples for GM (n) and results	Imaging results	Categorization (proven, probable, possible, no IPA)
Group I n=10*	n=10*- positive n=1 - negative	n=5 - negative	+	probable
Group II n=5	n=5 - negative	n=5 - positive	+	probable
Group III n=1	n=1 - positive	n=1 - positive	+	probable
Group IV n= 36	n=36 - negative	n=8 - negative	+	possible
Group V n= 38	n=81** - negative	-	-	no IPA

*incl. two transplanted patients; **More than one serum samples per patient were tested.

clinical features for IPA (n=36; 40%) (group IV), were considered with possible IPA.

Initially evaluated according to EORTC/MSG criteria from 2008, three serum samples, collected from three patients in group V, demonstrated OD index between 0.5 and 0.7, and 78 samples – OD index <0.5. When retested all 38 patients in this group were confirmed negative according to both older and updated criteria in 2020. The negative GM test results, the lack of positive imaging results and clinical features, classified all these patients in the non-IPA group (n=38; 42.2%).

None of the studied cases were categorized as proven IPA.

Aspergillus spp. was not isolated from any of the cultivated BAL samples.

None of the patients with possible IPA received antifungal therapy. The GM test remained negative on follow up.

Antifungal therapy was administered to all 15 patients with a positive GM result, determined as cases of probable IPA (9 from group I and all from group II and III). Voriconazole was used for 12 patients at a standard dose of 6 mg/kg loading dose followed by 4 mg/kg for a median pe-

riod of 12 days (4-27 days). Three patients were treated with liposomal amphotericin B at a dose of 3 mg/kg for a median period of 20.5 days (15-56 days).

Twelve of all patients who received antifungal therapy died: nine patients with acute leukemia, two with non-Hodgkin's lymphoma and one with Hodgkin's disease. IPA was the immediate cause of death in 3 cases (25%), all with acute leukemia. The other causes of death were progression of the hematological disease (n=3), other infectious complications (n=2), cerebral hemorrhages (n=2), therapy-related toxicity (n=1), and acute graft vs. host disease (n=1).

DISCUSSION

The invasive disease caused by *Aspergillus* moulds is one of the most severe complications in neutropenic patients with hematological malignancies and those with HSCT. The early detection and the rapid initiation of etiological therapy are of essential importance for the patient outcome, therapeutic success, and mortality prevention.[10]

The IPA incidence in patients with haematological malignancies and HSCT varies, but mean values reach 12%–15%.[2,11-15] In our study, the frequency of IPA in the selected tested patients is 16.6% (n=15).

A large-scale retrospective multi-center study[16] conducted to characterize better the invasive mycotic infections in patients with hematological malignancies without HSCT demonstrated that the highest rate (94% of cases) of IPA was observed in patients with acute leukemia (myeloid and lymphoid). The same study reported that patients with acute leukemia were at a higher risk for developing IPA and its complications. Similarly, we found that 61.5% of our patients with positive GM test were with acute leukemia.

In the present study, 10.5% of the patients with positive GM test were allogeneic transplanted patients. According to the literature, the incidence of IPA in individuals with HSCT varies. Depending on the transplant center, the incidence of IPA among patients undergoing allo-HSCT varies from 4 to 24%, with most studies reporting 8 – 15%. Unlike allo-HSCT, the incidence of IPA after auto-HSCT is significantly lower, ranging from 1 to 2%.[17] The mortality rate associated with IPA in HSCT recipients can reach the dramatic 50-80%.[18]

Applying the revised and updated EORTC/MSG criteria, one false-positive result was detected. This patient was followed up, retested and later gave negative result. One of the possible explanations for this phenomenon is the fact that at the time of the microbiological examination, the patient was treated with piperacillin/tazobactam. Similar to our observations, other authors report false-positive results associated with parenteral administration of piperacillin/tazobactam or with amoxicillin/clavulanic acid.[19-21] Other reasons for false-positive GM results have also been described. Besides *Aspergillus* spp., other clinically important fungi (*Fusarium* spp, *Penicillium* spp, *Histoplasma capsulatum*) also possess galactomannan in their cell envelope. In cases of infection, caused by these organisms, due to cross-reactivity, the serum GM test may be false-positive.[22-24]

Six patients, included in our study, gave positive results in their BAL samples, but only one of these patients also had a positive serum sample. Numerous studies have been conducted to study the clinical relevance of the GM test in BAL fluids.[25-28]

Since the lung is the site of the primary infection, it is believed that the emergence of GM in BAL precedes its appearance in the blood circulation.[29] Bergeron et al.[25] conducted a study to detect GM in BAL fluid samples obtained from high-risk patients with hematological diseases and reported an average sensitivity (57.6%) and high specificity (95.6%) of the test. In a comparative study, Boch et al.[26] reported much higher sensitivity for BAL GM test (85%) compared to serum GM test (23%) and specificity of 88% for both tests. According to the 2017 ESCMID-ECMM-ERS guidelines[30], the detection of GM in BAL fluid samples has excellent performance, reaching sensitivity and specificity of 100% and 90.4%, respectively, when appropriate OD indices are used.

In addition, Hope et al.[31] demonstrated in experimental conditions that the GM values in BAL rise earlier after the onset of IPA than in the serum. The advantage of the GM test in BAL fluid is that the antimycotic therapy started before the microbiological examination does not affect the test and lead to no false-negative results.[27] The disadvantages are mostly associated with false-positive results in cases when beta-lactam antibiotics are used or in cases of mould colonization of the respiratory tract but with no development of a clinical disease.[32] Fisher et al.[27] concludes that use of both serum and BAL GM tests, together with clinical data, can substantially improve the IPA diagnosis. It should be noted that collecting BAL fluid samples in critically ill patients or patients with hematological malignancies is associated with high risk of complications such as bleeding, respiratory failure or pneumothorax.[33]

In our study, the patients at risk for infectious complications were routinely screened for invasive aspergillosis without initiating prophylaxis. Antifungal therapy with voriconazole or liposomal amphotericin B was started in 15 patients, determined as cases of probable IPA.

In this study, twelve of the treated patients died, but only in three of the lethal cases (25%) IPA was the immediate cause of death. Even after the introduction of several new agents with anti-mould activity, the mortality rates of IPA still remained high, varying from 50% to 90%.[5] Although the all case mortality rate of the patients with positive GM test is 80%, IPA is the immediate cause of death in 25%. Our results demonstrate that the mortality rate associated with IPA in this study is lower than in other European centres. In a single institution prospective survey from 2004 to 2009, Nicolle et al.[34] found that the mortality at month one and month three in patients with hematological malignancies after IPA was 13% and 43%, respectively. In addition, another prospective Italian

study[35] which included allo-HSCT patients reported mortality rate of 46.3% after IPA.

CONCLUSIONS

To the best of our knowledge, this is the first study in Bulgaria evaluating the clinical significance of GM test for the diagnosis of IPA in patients with hematological malignancies, including patients undergoing HSCT.

IPA is an infectious disease with severe course and high mortality rates. The rapid diagnosis and the immediate launch of adequate antimycotic therapy are of crucial importance for the course and outcome of the disease. Aspergillus Galactomanan Enzyme-Immuno Assay is a reliable method that can be used both for diagnosis and monitoring the response to anti-mould therapy in cases of IPA, as well as a screening tool in neutropenic patients with different risk factors. The disadvantages of the test are mostly associated with the false-positive results in cases in which the patients receive either piperacillin/tazobactam or amoxicillin/clavulanic acid. The application of the revised and updated EORTC/MSG criteria published in 2020 allows more precise and correct identification of IPA, decreasing the rate of false-positive results in patients treated with beta-lactam antimicrobial agents. In the absence of contraindications, the simultaneous examination of serum and BAL fluid is recommended. The use of both serum and BAL GM tests, the regular monitoring of patients by the Aspergillus GM test, together with imaging results and clinical data improves significantly the IPA diagnosis.

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Инвазивный лёгочный аспергиллёз у пациентов с гематологическими злокачественными новообразованиями и трансплантацией гемопоэтических стволовых клеток: одноцентровое исследование

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Резюме

Цель: Целью этого исследования было оценить клиническую значимость теста на антиген *Aspergillus* Galactomannan (GM) для диагностики инвазивного легочного аспергиллёза (ИЛА) у пациентов с гематологическими злокачественными новообразованиями, включая пациентов, перенёсших трансплантацию гемопоэтических стволовых клеток (ТГСК).

Материалы и методы: С января 2016 г. по июнь 2019 г. девяносто пациентов прошли тестирование на GM. В общей сложности 134 образца крови и 19 образцов бронхоальвеолярного лаважа (БАЛ) были проанализированы с помощью иммуноферментного анализа Platelia *Aspergillus* Ag (лаборатории Bio-Rad). Средний возраст пациентов составлял 63 года (от 25 до 81 года). 56 пациентов (62.2%) были мужчинами. На основании результатов GM все пациенты были разделены на 5 групп.

Результаты: Положительный тест на GM -антиген был обнаружен у 16 пациентов (17.7%). У десяти из них были положительные образцы сыворотки (группа I). При повторном обследовании 1 пациент из 1-й группы дал отрицательный результат. Пять пациентов с отрицательными образцами сыворотки имели положительные результаты БАЛ (группа II). У одного пациента были положительные образцы сыворотки и БАЛ (группа III). Пятнадцать GM-положительных пациентов (9 из группы I, группы II и III) были отнесены к категории вероятных случаев ИЛА. Тридцать шесть пациентов (40%) с отрицательным результатом на GM (группа IV) считались вероятными случаями ИЛА. ИЛА был исключен у 38 (42.2%) пациентов (V группа). Противогрибковая терапия была назначена всем 15 пациентам, которые считались вероятными случаями ИЛА. ИЛА явился непосредственной причиной смерти в 3 случаях (25%).

Заключение: Наши результаты показали клиническую применимость скринингового теста GM ИЛА у пациентов из группы высокого риска с гематологическими злокачественными новообразованиями и ТГСК.

Ключевые слова

ELISA, галактоманнан, инфекция плесени, онкогематология, трансплантация стволовых клеток