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Multiple myeloma as a major cause of false-positive galactomannan tests in adult patients with cancer

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Summary *Objectives:* The galactomannan (GM) test is a useful method for early diagnosis of invasive aspergillosis. Recently, multiple myeloma has newly been suggested to be related to false-positive results of GM. We performed a case-control study to validate this finding.
Methods: Electronic medical records were reviewed for patients admitted March through June 2014. Patients with false-positive GM results were selected as cases and those with negatives as controls. To verify the results of the four-month analysis, additional analysis was performed in multiple myeloma patients over a three-year period.
Results: There were 30 false-positive and 316 negative cases during the four-month period. Among the factors evaluated, multiple myeloma was the only significant factor in the adjusted analysis (OR = 3.59, CI 1.28–10.04). In the three-year analysis of 145 multiple myeloma patients, 25.5% showed false-positive results, which was 3 times higher than overall. GM false-positivity was not related to serum monoclonal protein level or type of immunoglobulin. GM optical density indexes (ODIs) in all false positives were lower than 3.0.

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Conclusions: Multiple myeloma was a major cause of GM false-positivity in adult cancer patients. GM was false-positive in 25.5% of multiple myeloma patients with GM ODIs lower than 3.0.

Introduction

The presence of galactomannan (GM), a fungal antigen produced by *Aspergillus*, is a validated mycological criterion for diagnosing probable invasive aspergillosis (IA).[1,2] This method is very useful for diagnosing early IA in neutropenic patients, but various factors can cause false-positive results, including beta-lactam antibiotics, graft-versus-host-disease (GVHD), enteral nutrition, or specific parenteral fluid.[3–16] Among these, piperacillin/tazobactam was previously considered a major cause of GM false-positivity, but recent products of piperacillin/tazobactam are reported not to be related to it.[16–19] Meanwhile, multiple myeloma has begun to receive controversial attention as another cause of false-positivity.[20,21] To validate these recent findings and identify other possible causes of GM false-positivity, we performed a case-control study in adult patients with cancer admitted at a tertiary care university hospital.

Methods

Study design and patient selection

A case-control study was designed to evaluate the effects of antibiotic use and underlying malignancies on GM false-positivity in adult patients with cancer. We reviewed the electronic medical records (EMRs) of cancer patients who were admitted and tested for serum GM from March through June 2014 at Samsung Medical Center, Seoul, Republic of Korea. This tertiary care university hospital and referral center has 1950 beds, including the 700-bed Samsung Comprehensive Cancer Center. We included patients with either solid tumors or hematologic malignancies who were older than 16 years of age at the time of the GM test. Patients with false-positive GM results were selected as cases and those with negative results as controls. Patients who had been taking mold-active agents before the test and those who expired or were lost to follow-up within 1 month after the test were excluded from the analysis.

To verify the outcome of the four-month analysis, we performed additional review of EMRs of multiple myeloma patients who were admitted and tested for serum GM between July 2011 and June 2014. Patients with multiple myeloma older than 16 years of age at the time of the GM test were included. Case definition and exclusion criteria were the same as described above.

Data collection

We collected the following data from the EMRs: age, gender, date of admission, date of GM test, value of GM optical density index (ODI), antibiotics administered within 24 h prior to the GM test, underlying disease, and host factors for invasive fungal disease (IFD) according to EORTC/MSG guidelines.[1] For patients with multiple myeloma, serum monoclonal protein levels and immunoglobulin and light chain types were also evaluated.

Definitions

In this study, false-positive result of GM test was defined if the case met all of the following criteria: (1) the GM test was positive (ODI $\geq$ 0.5),[2] (2) the patient did not meet the criteria for probable or proven IA established by the EORTC/MSG,[1] and (3) the patient did not require mold-active agents within 1 month after the test. A GM test was considered true-positive if the case met the criteria for probable or proven IA according to EORTC/MSG guidelines.

Serum GM antigen test

Serum GM was measured using an enzyme-linked immunosorbent assay (ELISA)-based kit (Platelia Aspergillus; Bio-Rad Laboratories, Hercules, CA), following the manufacturer's instructions. Screening GM tests were performed once unless the results were positive. Symptomatic patients or those with positive GM results were tested two or three times a week according to clinicians' decisions. Performing imaging tests including high-resolution chest computed tomography (HRCT) for patients with positive GM results was also decided by clinicians depending on clinical course and host factors for IFD of the patient.

Statistical analysis

Student's *t*-tests and Mann–Whitney U tests were used to compare continuous variables, and chi-square tests and Fisher's exact tests were used to compare categorical variables. We used a logistic regression model to adjust for possible confounding factors. All *P*-values were two-tailed, and those <0.05 were considered to be statistically significant. SPSS for Windows (IBM, Armonk, NY, USA) version 20.0 was used for all statistical analyses.

Results

Baseline characteristics, antibiotic exposure, and GM ODIs

During the study period, 437 patients were admitted and tested for serum GM. 72 patients were excluded from the analysis; 23 were already on mold-active agents and 49

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