Association between Incidence of *Aspergillus* Antigenemia and Exposure to Construction Works at a Hospital Site*

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Summary

During the course of extensive building activity in the vicinity of bone marrow transplantation wards, the patients were routinely screened for the occurrence of *Aspergillus* galactomannan antigen in serum. In 19 (6.7%) out of 285 patients, an antigenemia was detected. Eleven (58%) of the 19 antigenemic patients suffered from autopsy-proven or clinically suspected invasive aspergillosis. The yearly incidence of antigenemic patients differed significantly, ranging from 0% in the year without building activities to 20.9% in the year with major activities, particularly interior completion works and landscaping. It is concluded that *Aspergillus* antigen monitoring of bone marrow transplant recipients has a limited value for the diagnosis of manifest invasive aspergillosis. However, it is epidemiologically useful to assess the extent of intensive contact with aspergilli and to control the effectivity of preventive measures.

Introduction

*Aspergillus* species are opportunistic pathogens, and they are widely distributed in the environment (6). Pulmonary infections are usually acquired through inhalation of *Aspergillus* conidia, which are universally present in unfiltered air (16). Severely immunosuppressed or neutropenic patients, especially those undergoing allogeneic bone marrow transplantation, carry the highest risk to develop invasive pulmonary or disseminated aspergillosis (5, 8, 25). The difficulties in the diagnosis and treatment result in an overall mortality of more than 50%; the mortality of patients after bone marrow transplantation can be as high as 95% (4). Clinical reports show, however, that the incidence of aspergillosis differs greatly worldwide, at different treatment centres and even within the same institution, ranging from as low as 0% to 25% or more (4).

One crucial factor influencing the variable incidence of aspergillosis is the degree of environmental exposure (4, 12). Particularly high numbers of *Aspergillus* conidia may be released during construction work, and an association between nosocomial out-

* Dedicated to Prof. Dr. H. Brandis on the occasion of his 80th birthday.
breaks of aspergillosis and building work on, or near, hospital sites are well document-
ed (2, 7, 9, 17, 18, 20, 22). During the course of such building activity, it is necessary, therefore, to intensify the protective measures and the surveillance of patients which are exposed and at risk of acquiring Aspergillus infections.

Recent approaches taken in an effort to improve the diagnosis of manifest aspergillosis include the detection of circulating Aspergillus galactomannan antigen in serum (10, 19, 24), and a latex agglutination test based on a monoclonal antibody (Pastorex Aspergillus; Sanofi, Diagnostics Pasteur, France) has become available commercially. At the University Hospital of Essen, Germany, the test was introduced into the routine microbiological surveillance programme of bone marrow transplant recipients coincidently with the beginning of an extensive building activity in the very near vicinity of the transplantation wards. The antigen monitoring was continued during the building period and more than one year beyond completion.

The present evaluation of test results obtained during a period of four years was performed to investigate the diagnostic and epidemiological value of screening for Aspergillus antigenemia in high-risk patients exposed to building work.

Materials and Methods

Patients. The study comprises 285 patients undergoing allogeneic bone marrow transplantation in the years 1991–1994 at the University Hospital of Essen, Germany. The patients were protected by laminar air flow tents or by barrier nursing, apart from those occasions when they were transported to different parts of the hospital for investigative procedures. All patients received antifungal drugs. As a rule, systemic prophylaxis with fluconazole given orally was initiated two weeks before transplantation and was continued intravenously during neutropenia. Fluconazole was replaced by intravenous amphotericin B when fever occurred, particularly if fever had failed to respond to antibacterial agents. In addition, non-absorbed polyene antifungal agents were included in the regimen of oral digestive tract decontamination. Within the regular microbiological surveillance programme, serum was tested once or twice a week for Aspergillus antigen. The diagnosis of invasive aspergillosis was categorized as follows: (i) proved infection: histological demonstration of branched hyphae and culture of Aspergillus from autopsy samples; (ii) probable infection: fever of > 38°C for more than five days, unresponsive to fluconazole and systemic antibacterial agents but responsive to systemic amphotericin B, presence of pulmonary infiltrates, and no evidence of other fungal aetiology.

Detection of Aspergillus antigen in serum. The latex agglutination test Pastorex Aspergillus (Sanofi, Diagnostics Pasteur, France) was carried out according to the manufacturer’s instructions and as described before (1).

Building works. From January 1991 to September 1993, a 3-storey complex, covering an area of about 3704 m², was erected at the hospital premises for use as a new bone marrow transplantation unit. In October 1993, the first patients were hospitalized in the new building. The old bone marrow transplantation wards were located close to the construction area. The front site has a distance of approximately 75 m to the new building, and the rear site faces the road where all the building traffic must pass through. During the construction period of the new building, the old transplantation unit was in full operation.

Results

From 285 bone-marrow transplant recipients, 4818 serum specimens were investigated for Aspergillus antigen (Table 1). Fifty-six (1.2%) sera reacted positively, i.e. in
Table 1. Association between *Aspergillus* antigenemia and exposure to building works in bone marrow transplant recipients

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of patients surveyed</th>
<th>No. of serum specimen</th>
<th>No. of patients with antigenemia</th>
<th>Major building works in the vicinity of the patients</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>total</td>
<td>antigen positive</td>
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<tr>
<td>1991</td>
<td>75</td>
<td>1063</td>
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<td></td>
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Earth removal, foundation laying

Erection of framework, concrete pouring

Interior completion, landscaping

No building works
19 (6.7%) of the patients an *Aspergillus* antigenemia was detected. Of these 19 antigenemic patients, 4 patients developed a lethal aspergillosis, and in 7 patients, aspergillosis was suspected clinically. The positive predictive value of the antigen test for proved and probable invasive aspergillosis amounted to 58%, and for proven aspergillosis alone not more than 21%. Eight of the 19 antigenemic patients showed no sign of invasive aspergillosis, i.e. 42% of the test results were false-positive in regard to manifest disease.

The frequency of antigen-positive serum specimens varied considerably (Table 1). Between 1063 and 1402 serum samples were investigated each year, and whilst the rate of positive samples was <0.4% in the years 1991, 1992, and 1994, the rate of positive samples rose to 4% in 1993. The increase was even more pronounced when the incidence of antigenemic patients is regarded. In 1993, 14 (20.9%) of the 67 patients treated in that year developed antigenemia. The figures for the years 1991, 1992, and 1994, however, were 4%, 3%, and 0%, respectively. The difference between 1993 and the other years is statistically significant (p = <0.001).

No significant variation of the patient population, the treatment and nursing regimens, or the climatic conditions, factors that may influence the incidence of *Aspergillus* infections, occurred during the years 1991–1994. However, the building activities in the vicinity of the bone marrow transplantation unit changed during that period (Table 1). From January 1991 to February 1993, the ground preparation and the shell construction of the new building were carried out. In this time, 5 (26.3%) of the 19 antigenemic patients were recorded. From March 1993 to September 1993, the internal completion works and the landscaping were done, i.e. the building traffic and the number of companies and workers involved increased. Coincidentally, 13 (68.4%) of the 19 antigenemic patients were found in this period. One patient admitted during the final phase of construction work became antigenemic one month after completion. The strong association between the frequency of antigenemic patients and the exposure to building activities is further corroborated by the finding that none of the 71 patients admitted in the year 1994, i.e. after termination of construction work, and hospitalized in the new transplantation unit developed *Aspergillus* antigenemia.

Discussion

The first evaluation of the *Aspergillus* latex agglutination test revealed a sensitivity of 93.3–94.4% for proved and probable aspergillosis and a specificity of 100% (10). However, the hope to have a substantial improvement of the diagnosis of invasive aspergillosis was not corroborated by later studies. They showed a sensitivity of 36%–50% and a specificity of 53%–100% (1, 13, 15, 21). The low positive predictive value of 58%, and the rate of 42% false-positive results found in the present study underline that the antigen test is of limited value for the diagnosis of manifest invasive aspergillosis.

False-negative test results can be explained by the transient presence of galactomannan antigen in serum (3). The relatively prolonged excretion of antigen in urine may yield a higher diagnostic sensitivity (1). False-positive test reactions may be caused by various factors, e.g. technical errors (23) and fungal contamination of serum samples (14). Excluding those artifacts, it is fairly certain that a positive reaction of serum indicates the presence of circulating *Aspergillus* galactomannan antigen. Though an antigenemia is not a specific sign of manifest invasive aspergillosis, it reflects at least in-
tensive contact with Aspergillus, i.e. colonization or latent infection. This contact should be prevented in neutropenic patients, because the final outcome is unpredictable and often fatal (1).

Building activities are generally regarded as a source of Aspergillus conidia and as an infection risk for susceptible patients. However, whether or not a particular building work or a special procedure or any other environmental event generate large numbers of conidia endangering patients, is hard to assess. Weekly monitoring of conidial counts by air sampling during the course of extensive building activity showed no apparent correlation with any form of building work (11). Continuous monitoring of ambient conidia levels would be necessary to record with any certainty transient clouds of conidia. Despite such an effort, the determination of the environmental conidia counts cannot be relied upon as a simple predictor of infection risk because exposure to conidia may or may not result in colonization or infection. Better than environmental counts, assessment of nasal carriage reflects both exposure to conidia and attack rate (11). The present study shows that screening for Aspergillus antigenemia is also a useful epidemiological tool for monitoring the true Aspergillus burden of patients.

The variations in the frequency of antigenemia from year to year indicate that a rate of up to 4% of antigenemic patients represents the basic risk of Aspergillus contacts in bone marrow transplantation recipients which are treated under the common protective measures. An increase of the incidence reflects either insufficient protection or an unusually high Aspergillus pressure from the environment. As neither the protection nor the treatment regimens were changed during the study period, the drastic increase of the rate of antigenemic patients to 20.9% in the year 1993 must be attributed to unusually high ambient Aspergillus levels during this period. The temporal coincidence of the increase with major building activities does not prove but makes it most probable that the building activities, particularly the interior completion works and landscaping, were the source of the high degree of Aspergillus contamination that caused the antigenemias. Obviously, this environmental pressure overwhelmed the protective isolation, barrier nursing, and antifungal chemoprophylaxis, that had been a sufficient preventive strategy under normal environmental conditions.

In conclusion, despite the limited value of the Aspergillus antigen test in the diagnosis of manifest aspergillosis, it seems to be epidemiologically useful to monitor the environmental exposure of high risk patients to aspergilli and to assess the effectivity of preventive measures. Routine screening should be performed in bone marrow transplant recipients to maximise the chances of diagnosing invasive aspergillosis and to control preventive strategies.

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References


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