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Nonspecific elevation of serum *Aspergillus* galactomannan antigen levels in patients with rheumatoid arthritis

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ABSTRACT

Background: Infections are an important cause of morbidity and mortality in patients with rheumatoid arthritis. Patients receiving immunosuppressive or anti-tumor necrosis factor (TNF) agents are vulnerable to fungal infections, including those derived from *Aspergillus* species. Detection of the *Aspergillus* galactomannan antigen in serum is useful for the early diagnosis of invasive aspergillosis in patients with hematological malignancies. However, its usefulness for detecting early invasive aspergillosis in rheumatoid arthritis patients remains unestablished.

Methods: Galactomannan antigen levels were measured in 340 patients (311 female patients). For patients who exhibited galactomannan antigen levels ≥ 0.5 during the initial examination, a second examination was performed 3–6 months later. Conventional blood tests and chest radiography were also performed.

Results: Elevated galactomannan antigen levels (≥ 0.5) were observed in 62 (18.2%) of 340 patients during the initial examination. A second examination was performed in 56 of 62 patients, 50 of whom exhibited elevated antigen levels. Elevated antigen levels were not associated with the use of any drug including anti-TNF agents. Serum galactomannan antigen levels were correlated with the albumin/globulin ratio ($r=-0.19$, $p<0.001$), γ-globulin (%; $r=0.17$, $p=0.001$), and hemoglobin concentration ($r=-0.15$, $p=0.005$). No patient was clinically diagnosed with invasive aspergillosis during the study period.

Conclusions: Serum galactomannan antigen levels are frequently elevated in a nonspecific manner in patients with rheumatoid arthritis.

[1]M. Horie and H. Tamiya contributed equally to this study.

1. Introduction

Infections are an important cause of morbidity and mortality in patients with rheumatoid arthritis (RA) [1,2]; previous studies demonstrate the frequent occurrence of respiratory infections [3]. One proposed cause of the high prevalence of infections is the use of immunosuppressive drugs. *Aspergillus* species are some of the most important causative organisms of opportunistic infections, specifically invasive aspergillosis (IA), which is a serious and often fatal condition.

RA frequently affects the respiratory system, causing interstitial pneumonia, necrobiotic nodules, bronchiolitis, or pleuritis [4,5]. These disorders are likely to impede early detection of pleuropulmonary infection [6]. When IA is suspected on the basis of chest radiographs, demonstration of hyphal tissue invasion or recovery of the organism in culture is necessary for a definitive diagnosis [7]. Bronchofiberscopy is a common procedure for this purpose but often provides false-negative results. In addition, the incidence of normal and nonspecific chest radiographic findings is high during the early stages of IA [8]. To overcome the difficulties associated with early diagnosis using conventional methods, novel approaches including the detection of Aspergillus antigens or genomic DNA sequences have been developed [9,10]. Galactomannan (GM) is a heat-stable polysaccharide component released from the cell wall during hyphal tissue growth and is essential to the survival of *Aspergillus* [11]. *Aspergillus* GM antigen detection in serum or bronchoalveolar lavage fluid may be useful for the early diagnosis of IA in patients with hematological malignancies [12–14] or high-risk ICU patients [15]. However, false-positive results may arise under certain conditions [16].

Therefore, the present study evaluated the usefulness of serum GM antigen for the detection of pulmonary aspergillosis in patients with RA.

2. Materials and methods

2.1. Patients

A total of 340 consecutive patients (29 men and 311 women) aged 25–99 years (mean=64.8 years) who had visited a private rheumatology clinic in Tokyo participated in this study. Each patient met the 1987 ACR criteria for RA [17] and had been previously treated with various combinations of drugs (Table 1). All patients provided written informed consent to participate.

2.2. Protocols

The initial recruitment period occurred between January 1, 2008 and October 31, 2008; the follow-up lasted until March 31, 2009. Peripheral venous blood was drawn for analyses including complete blood cell count, C-reactive protein, erythrocyte sedimentation rate, albumin, γ-globulin, rheumatoid factor, and *Aspergillus* GM antigen. Rheumatoid factor was assayed using immunonephelometry; the normal range was $\leq$15 IU/mL. The GM antigen was assayed using Platelia *Aspergillus*® (Bio-Rad, Marnes-La-Coquette, France). The cut-off was set at 0.5; if the value was $\geq$0.5, it was remeasured 3–6 months later. Chest radiography was performed on the day of the blood test. Patients were assessed regularly at the clinic, and the occurrence of any serious event was recorded. Changes in the type of antirheumatic drugs administered for disease control were permitted. The use of intravenous piperacillin–tazobactam or oral amoxicillin clavulanate was avoided as much as possible; if used, blood collection was postponed for at least 1 month following cessation of antibiotic usage. X-ray films were assessed separately by 3 expert pulmonologists, and the results were accepted when an agreement was reached between any 2 of them. This study was approved by the Ethics Committee of Kanto Central Hospital (No. 19-5-003, November 8, 2007).

2.3. Diagnostic procedures and definition of IA

As the private clinic was not equipped with a CT scanner, which is the gold standard for diagnosing IA, chest radiography examinations were performed for IA screening from 3 to 6 months. When no abnormal change was observed on both chest X-ray films, IA was ruled out. If patients exhibited new abnormal shadows on the chest X-ray image, such as a consolidation, cavity, or nodule, or had new symptoms such as fever, chest pain, cough, or hemoptysis, they were immediately referred to the Kanto Central Hospital, and further examinations for IA diagnosis, including microbiological cultures, chest CT, and bronchofiberscopy, were performed according to the EORTC/MSG definition of invasive fungal disease [18]. No patient was suspected of having IA throughout the study period.

Abbreviations: GM, galactomannan; TNF, tumor necrosis factor; IA, invasive aspergillosis; RA, rheumatoid arthritis; RR, relative risk

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