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Immune reconstitution inflammatory syndrome in neutropenic patients with invasive pulmonary aspergillosis

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Summary *Objectives:* Clinical and radiologic deterioration is sometimes observed during neutrophil recovery in patients with invasive pulmonary aspergillosis (IPA). This deterioration can be caused by immune reconstitution inflammatory syndrome (IRIS) as well as by progression of the IPA. However, there is limited data on IRIS in neutropenic patients.
Methods: Over a 6-year period, adult patients with neutropenia who met the criteria for probable or proven IPA by the revised EORTC/MSG definition were retrospectively enrolled. IRIS was defined as de novo appearance or worsening of radiologic pulmonary findings temporally related to neutrophil recovery, with evidence of a decrease of 50% in serum galactomannan level.
Results: Of 153 patients, 36 (24%, 95% CI 18%—31%) developed IRIS during neutrophil recovery. More of these patients received voriconazole than did those with non-IRIS (42% vs. 25%, $P = 0.05$). Thirty- and ninety-day mortalities were lower in the patients with IRIS than in those with non-IRIS (11% vs. 33%, $P = 0.01$, and 33% vs. 58%, $P = 0.01$, respectively).
Conclusion: IRIS is relatively common among neutropenic patients with IPA, occurring in about one quarter of such patients. It is associated with voriconazole use and has a good prognosis.

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Introduction

Invasive pulmonary aspergillosis (IPA) is associated with high morbidity and mortality in patients with hematologic malignancies who are undergoing myelosuppressive chemotherapy or receiving hematopoietic stem cell transplants.[1] Since alveolar macrophages and neutrophils play a dominant role in host defenses against aspergillosis,[2] neutropenia from chemotherapy or underlying hematologic disease is an important predisposing host factor for IPA. Sometimes clinical and radiologic deterioration is observed during neutrophil recovery in patients with IPA, and this deterioration can be associated with immune reconstitution inflammatory syndrome (IRIS) or with the progression of the IPA. Caillot et al. showed that the median volume of lesions in neutropenic patients with IPA, as measured serially by CT, increased four-fold from day 0 to day 7 despite antifungal therapy.[3] However, many physicians consider that worsening of the radiologic findings of IPA during neutrophil recovery is associated with progression of the infection and they modify the antifungal therapy with or without surgery.[4] However, if there is no microbiologic documentation, it is unclear whether this radiologic deterioration is associated with IPA progression or with IRIS. Recently, the GM assay has been proposed as a microbiologic marker of response.[5,6] If so, it might be possible to decide whether the radiologic worsening of IPA in neutropenic patients is due to IPA progression or immune reconstitution inflammatory syndrome (IRIS) by assessing clinical and microbiologic parameter as well as immunologic parameters such as neutrophil count. This distinction helps clinicians to guide antifungal therapy in this difficult clinical situation. In addition, this procedure could detect refractory IPA more objectively, and could advance clinical study of salvage therapy in refractory IPA without dilution of the results of studies by the inclusion of patients with IRIS.

The concept of fungal IRIS was originally proposed in patients starting antiretroviral therapy for human immunodeficiency virus (HIV) infection and was clearly demonstrated in those with cryptococcal infection, histoplasmosis, and candidiasis.[7] In non-HIV patients, cases of fungal IRIS have been reported in transplant recipients,[8–10] neutropenic patients,[11,12] and recipients of TNF-α receptor inhibitors.[13,14] Recently, Singh et al. reported that about 5% of solid organ transplant recipients with cryptococcal infections had IRIS-like illnesses, and these appeared to be associated with a certain immunosuppressive regimen.[9] In addition, Legrand, et al. showed that some neutropenic cancer patients with chronic disseminated candidiasis who were unresponsive to antifungal therapy and improved dramatically after corticosteroid therapy appeared to suffer from what they suggested to be fungal IRIS.[15] Miceli et al. proposed a similar concept of IRIS in patients with IPA; this was defined as the onset or worsening of clinical and radiological findings together with neutrophil recovery and a $\geq$ 50% decrease in serum GM titers that could not be explained by newly acquired infection, failure of treatment, or side effects of treatment.[4] They described 19 neutropenic non-HIV patients conforming to this definition of fungal IRIS.[4] However, data are limited on the incidence, clinical characteristics, and outcomes of IRIS associated with IPA in neutropenic cancer patients. We therefore evaluated the incidence, clinical characteristics, and outcomes of IRIS in neutropenic patients with IPA.

Patients and methods

Study population and data collection

This study was performed at the Asan Medical Center, a 2700-bed tertiary care teaching hospital in Seoul, South Korea. The medical records of adult patients ($\geq$ 16 years old) with neutropenia who met the criteria for proven or probable IPA from January 2008 to December 2013 were retrospectively reviewed.

Definitions

Patients were assigned a proven or probable diagnosis of IPA based on a modification of the consensus definition of EORTC/MSG and our previous studies.[1,16–20] Proven IPA was defined by histologic evidence of tissue invasion including septated, acutely branching filamentous fungi and positive culture or positive GM assay. Probable IPA was defined as the presence of host factors, together with one or more clinical indication such as dense, well circumscribed lesions with or without a halo sign, and an air-crescent sign, or cavity on CT; and mycologic evidence of fungal infection (by culture or cytologic analysis of bronchoalveolar lavage fluid for *Aspergillus* species, or GM assay of serum or bronchoalveolar lavage fluid). Possible IPA was defined as the presence of a host factor and clinical criteria without mycologic evidence for IPA. Cases classified as possible IPA were not included in this analysis.

Neutropenia was defined as an absolute neutrophil count $<$500 cells/mm^3, and neutrophil recovery was defined as a neutrophil count of $\geq$500 cells/mm^3 for 2 consecutive days.[21] Corticosteroid use was defined as use of a mean minimum dose of 0.3 mg/kg/day of prednisolone equivalent for $>$3 weeks.[1] Immunosuppressant use was defined as treatment with a T-cell immunosuppressant such as cyclosporin, TNF-α blocker, specific monoclonal antibody (such as alemtuzumab), or purine analogs during the previous 90 days.[1] Serum GM antigen levels were measured as described previously (Platelia Aspergillus EIA; BioRad, Redmond, WA).[18,19] They were considered positive if the GM index was $\geq$0.5 serum GM antigen level.

IRIS was defined as new or worsening radiologic pulmonary findings temporally related to neutrophil recovery, with evidence of a 50% decrease in a single serum GM index titer combined without evidence of persistent positive fungal culture and absence of new extrapulmonary lesions of aspergillosis (e.g., new skin lesions) and other problem, such as newly acquired infection, failure of treatment of a known infection, or side effect of medication.[4] Clinical response to antifungal therapy was classified as success (complete or partial response) or failure (stable response, progression of disease, or death) as described previously[22] and assessed 10 days after neutrophil recovery (if a patient died before neutrophil recovery, failure was assigned to the day of death), 1 month, and 3 months after diagnosis,