Invasive filamentous fungal infections in allogeneic hematopoietic stem cell transplant recipients after recovery from neutropenia: Clinical, radiologic, and pathologic characteristics

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Abstract

Invasive filamentous fungal infection (IFFI) is an important cause of mortality in allogeneic hematopoietic stem cell transplant (HSCT) recipients. We reviewed 22 consecutive cases of IFFI in allogeneic HSCT recipients at Roswell Park Cancer Institute. IFFI was diagnosed after neutrophil recovery in 21 patients (95%). All had received corticosteroids within 1 month prior to IFFI diagnosis. Fourteen (64%) presented with dyspnea, and only 7 (32%) were febrile. Aspergillus species were isolated in 18 (82%) cases. Thirty day mortality after IFFI diagnosis was associated with a higher mean daily dose of corticosteroids \( P = 0.02 \) and receiving OKT3 \( P = 0.01 \) within 1 month prior to IFFI diagnosis and serum creatinine > 2 mg/dl at the time of diagnosis \( P = 0.004 \). Histopathologic material from biopsy or autopsy was available in 15 patients (68%). In 8 (53%), the predominant lung histopathology was an acellular coagulative necrosis and hyphal angioinvasion was observed in some of these cases. These findings have generally been observed in neutropenic patients but not in non-neutropenic HSCT recipients. The predominance of coagulative necrosis in our series may reflect the high doses of corticosteroids used to treat graft-versus-host disease (GVHD), which may have disabled leukocyte trafficking and hyphal killing.

Key words: Aspergillus, filamentous fungal infection, histology, transplantation

Introduction

Prolonged and persistent neutropenia is a critical risk factor for invasive aspergillosis [1]. However, among allogeneic hematopoietic stem cell transplant (HSCT) recipients, most cases of invasive filamentous fungal infection (IFFI) occur after neutrophil recovery, in the setting of potent immunosuppressive therapy for graft-versus-host disease (GVHD).

Animal models of invasive aspergillosis and experience in patients suggest that Aspergillus infection during neutropenia is pathologically and immunologically distinct from infection in the absence of neutropenia in the setting of potent immunosuppressive regimens used to treat GVHD. In order to assess whether the host pattern of IFFI is applicable in a large cancer referral center, we performed a retrospective analysis of 22 consecutive cases of IFFI in HSCT recipients at Roswell Park Cancer Institute, Buffalo, NY. All transplants were allogeneic and all but one case were diagnosed after resolution of neutropenia. Our specific goals were to define the clinical, radiologic, and
pathologic manifestations of IFFI in the late transplant period, to contrast these findings with those typically associated with neutropenia, and to identify variables predictive of survival.

There are sparse data about the histopathology of IFFI in HSCT recipients after neutrophil recovery. In our series, the predominant histopathologic finding was coagulative necrosis, which is a characteristic feature of IFFI in neutropenic patients but usually not thought to be associated with IFFI in non-neutropenic HSCT recipients. This may have important implications about the effect of high-dose corticosteroids on leukocyte trafficking and hyphal killing.

Methods

Study populations. We conducted a retrospective study of 22 HSCT recipients with IFFI at Roswell Park Cancer Institute between January 1995 and December 1999. Twenty-four HSCT recipients with mould isolates were identified by our microbiology database. Twenty-two of these patients met our prospectively defined criteria for proven or probable fungal infection. All of the transplants were allogeneic.

Proven filamentous fungal infection was defined as recovery of the mould from a normally sterile site and/or documentation of invasive disease by histopathology. One limitation of our study is that because patients were screened by mining our microbiology database, patients with proven IFFI based on histopathology but with negative cultures, were not included. Probable infection was defined as a positive mould culture from the sinopulmonary tract plus compatible radiographic findings, but absence of histopathologic documentation of invasive disease. This definition requires a positive culture, and therefore may be more stringent than recently published consensus diagnostic criteria for IFFI, in which a positive mould culture or galactomannan assay fulfills the microbiologic criteria for “probable” aspergillosis [2]. Disseminated infection was defined as recovery of mould isolates from 2 or more non-contiguous sites.

Data collection. The charts of all HSCT recipients in whom a mould species was isolated were reviewed. Relevant radiologic studies were reviewed by one author (PL). The pathologic material was reviewed by two of the authors (AS, BHS) and the findings were correlated with those in the original pathology reports in the hospital records. The reviewers were blinded to the original pathology report at time of review. The original findings were confirmed in all cases.

Statistical analysis. Survival curves were analyzed using the Kaplan–Meier method and the log rank test. The primary time point for survival analysis was 30 days after diagnosis of IFFI. This short-term endpoint was chosen because mortality during this period was most likely to be due to fungal infection. Long-term survival data were available on all patients from the time of IFFI diagnosis until December, 31, 2002. The Student’s t-test was used to compare means and the chi square and Fisher exact tests were used to compare proportions where appropriate. A P < 0.05 was considered to be significant. All tests were carried out using STATA software (Intercooled version 7.0; College Station, TX).

Results

Demographic data and clinical manifestations of IFFI

Twenty-two HSCT recipients meeting the criteria for IFFI were identified. Patient characteristics are summarized in Table 1. All patients had hematologic malignancies. Seven patients (32%) had acute myelogenous leukemia, 6 (27%) had chronic myelogenous leukemia, 3 (14%) had myelodysplastic syndrome, 5 (23%) had non-Hodgkin lymphoma, and 1 (5%) had acute lymphocytic leukemia. All had received an allogeneic transplant, including three who were cord blood transplant recipients.

The interval from transplantation to IFFI diagnosis ranged from 1 to 28 months, with a median of 142 days. There were no obvious differences in clinical, radiographic, or pathologic manifestations of IFFI in patients diagnosed with IFFI prior to and after 142 days. IFFI was diagnosed within 1 year of transplant in 20 patients