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Fatal cytomegalovirus pneumonia in patients with haematological malignancies: an autopsy-based case–control study

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ABSTRACT

Cytomegalovirus (CMV) pneumonia is a life-threatening infection in patients with haematological malignancies (HMs) or in haematopoietic stem cell transplant (HSCT) recipients. To assess the incidence and risk factors for developing fatal CMV pneumonia in these patients, a case–control study based on 999 autopsies was performed at The University of Texas M. D. Anderson Cancer Center, Houston, Texas (January 1990 to December 2004). Twenty-five cases (patients who died with CMV pneumonia) were matched with 34 controls (patients who died without CMV pneumonia) by type of HM or HSCT, year of autopsy, age and gender. The incidence of CMV pneumonia declined between January 1990 to June /1997 and July 1997 to December 2004 (CMV pneumonia rates were 22/620 and 3/379 autopsies, respectively; p 0.006). Logistic regression analysis identified complete remission and sustained lymphopenia as independent predictors of CMV pneumonia (all p <0.05). The incidence of fatal CMV pneumonia has decreased over the last 15 years, which might reflect earlier diagnosis or the use of pre-emptive therapy or more effective preventive strategies. Complete remission of an HM does not preclude the development of CMV pneumonia among patients with prolonged lymphopenia.

Keywords Autopsy, cancer, cytomegalovirus, haematological malignancies, pneumonia

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INTRODUCTION

Cytomegalovirus (CMV) pneumonia is a frequently fatal infection in patients with haematological malignancies (HMs) and in those undergoing haematopoietic stem cell transplantation (HSCT); the disease-specific mortality rate varies from 30% in lymphoma patients, to 57% in those with leukaemia and up to 90% in those who have undergone HSCT [1–5]. Definitive diagnosis of CMV pneumonia relies on the detection of the virus in lung tissue; however, lung biopsies are rarely performed in patients with cancer because of the morbidity (e.g. bleeding) associated with this procedure [6,7]. Thus, studies of histopathologically proven CMV pneumonia in cancer patients have been limited. The serious consequences of CMV pneumonia in such patients, however, make it vitally important that we better understand and characterize the risk factors for infection.

The incidence of CMV disease revealed after autopsy of immunocompromised hosts ranges from 0.3% to 51% [8]. Data from autopsies of cancer patients who were not HSCT recipients at The University of Texas M.D. Anderson Cancer Center (MDACC) from January 1964 through December 1990 showed an increase in the incidence of CMV pneumonia [9]. Given this potentially large source of patient data, a case–control study of patients who had been autopsied at MDACC was designed, specifically to determine the incidence of, and the risk factors for, fatal CMV pneumonia in patients with HMs, including HSCT recipients.

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PATIENTS AND METHODS

The autopsy records of all patients in the MDACC autopsy registry who were reported to have died between January 1990 and December 2004 (n = 999) were reviewed. Patients with HMs or who were HSCT recipients were included in the study and categorized according to the absence (controls) or presence (cases) of CMV pneumonia at autopsy. The 25 cases were matched with 34 controls, primarily by type of HM or prior HSCT receipt (100% of cases) and secondarily by year of autopsy (85% of cases), patient age (74% of cases) and patient gender (74% of cases). Information on demographics, type of HM or HSCT, comorbidities (e.g. chronic lung disease or renal failure, autoimmune disorders, diabetes mellitus or hypogammaglobulinaemia), chemotherapy and corticosteroid treatment, disseminated CMV disease, concomitant infections, clinical and radiological signs of CMV pneumonia and antiviral treatment, were collected from the patients' medical records. The cause of death recorded in each autopsy report was noted. Human immunodeficiency virus-infected patients were included. Patients with solid tumours, however, were excluded. The study was approved by the MDACC institutional review board.

Definitions

Autopsy-proven CMV pneumonia was defined as the presence of CMV infection in lung tissue samples identified by characteristic intranuclear or intracytoplasmic viral inclusions with surrounding necrosis, inflammation or both. For most patients, sections of the lungs, lymph nodes, liver, spleen, adrenal glands and other tissues indicated to be of interest in the autopsy report were examined. The results of cultures performed at the time of the autopsies were obtained from records available in the microbiology laboratory. Culture identification tests for CMV (shell vial or conventional viral cultures) were performed on lung tissue samples of some patients as previously described [10]. Also, CMV antigenaemia—detection of the viral protein CMV pp65 in white blood cells—was performed in a small subset of patients. Neutropenia was defined as a neutrophil count of $<500/mm^3$. Lymphopenia was defined as a lymphocyte count of $<1000/mm^3$.

Therapy

Therapy for CMV pneumonia consisted of intravenous ganciclovir (5 mg/kg every 12 h) with or without intravenous immunoglobulin (500 mg/kg every other day). Foscarnet (60 mg/kg intravenously every 8 h) was substituted for ganciclovir in patients who experienced severe myelosuppression during ganciclovir therapy. The ganciclovir and foscarnet doses were adjusted as needed, depending on the creatinine clearance.

Statistical analysis

Case and control data were compared to identify possible predictors of the development of CMV pneumonia. Univariate analysis using Fisher's exact test was then used to assess the significance of differences between the two groups. Variables with p <0.1 and those found to be clinically relevant according to univariate analysis were then subjected to multivariate logistic regression analysis. Multiple logistic regression was used to assess the predictors of development of CMV pneumonia in cases and controls, to determine which factors were independent predictors of CMV pneumonia. All data were analysed using SAS software (SAS Institute, Cary, NC, USA) and Epi Info (version 3.2.2; CDC, Atlanta, GA, USA). Two-tailed p-values of <0.05 were considered to be statistically significant.

RESULTS

Incidence

From January 1990 through December 2004, 999 autopsies were performed at MDACC. CMV pneumonia was diagnosed after histopathological examination in 25 patients. The total incidence of CMV pneumonia at autopsy was 3% (25 of 999 autopsies), with a significant decline between the periods of January 1990 through June 1997 and July 1997 through December 2004 (22 of 620 (3.5%) and three of 379 (0. 8%) autopsies, respectively; p 0.006). The autopsy rate also decreased significantly between these two periods (620 of 4855 (13%) and 379 of 5001 (8%) deaths, respectively; p 0.0001).

Patients

The characteristics of patients with CMV pneumonia are given in Table 1. Most of the cases of pneumonia occurred in HSCT recipients (68%, mainly allogeneic) and lymphoma patients (20%, mainly non-Hodgkin lymphoma). No patient had underlying acute leukaemia. Three patients were infected with human immunodeficiency virus. Twenty of the 25 patients (80%) had received chemotherapy and 17 patients (68%) had been treated with corticosteroids (68%) within 6 months prior to autopsy. The majority of patients required admission to the intensive-care unit with respiratory and circulatory support (Table 1). The median number of days between the onset of first CMV-related symptoms and HSCT was 118 (Table 1).

CMV pneumonia was diagnosed *ante mortem* in 16 of 25 patients (64%) by detection of pulmonary infiltrate and identification of CMV in the lower respiratory tract (12 patients) or other sites (four patients). CMV pneumonia was clinically suspected before their death in 15 of these 16 patients. The lower respiratory tract samples were obtained by means of bronchoalveolar lavage