CYTOMEGALOVIRUS IgG AND IgM ANTIBODIES AMONG SUDANESE PATIENTS WITH ACUTE MYELOID LEUKEMIA: RELATION TO HEMATOLOGICAL PROGNOSTIC MARKERS

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ABSTRACT

Background: Viral oncogenesis has remained an area of interest in cancer biology. Viruses have been great tutors of cancer biology, helping researchers to uncouple many signaling pathways and identifying critical therapeutic targets. **Aim:** The aim of this study was to assess the incidence of cytomegalovirus (CMV) infection and its impact on hematological prognostic markers of Acute Myeloid Leukemia (AML) among Sudanese populations. **Method:** The seroprevlance of CMV infection in AML patients was assessed in 100AML and 100 age and gender-matched controls. The associations of total white cell count and absolute blast count with the seroprevlance were examined. **Results:** The prevalence of CMV infection was 81% in patients and 17% in control subjects. Total white cell count and blast count were higher in AML CMV positive patients than AML CMV negative patients. **Conclusion:** Our findings indicate a high incidence of CMV infections in AML and its worse association with hematological markers could emphasize the role of CMV in the progression of AML.

KEYWORDS: Acute myeloid leukemia, Cytomegalovirus.

INTRODUCTION

Acute myeloid leukemia myelogenous leukemia (AML) is a neoplastic disease of the myeloid hempoietic cells described by the accelerated growth of abnormal myeloblasts that accumulate in the bone marrow and blood and may infiltrate other organs. AML is the most common acute leukemia affecting adults, and its incidence increases with age [1]. Viral oncogenesis has remained an area of interest in cancer biology. Viruses have been great tutors of cancer biology, helping researchers to uncouple many signaling pathways and identifying critical therapeutic targets. With the advent of advanced molecular techniques, more viruses have been attributed to cause neoplasms in humans [2].

The role of infections in carcinogenesis is abundantly described. Human cytomegalovirus (HCMV) is a ubiquitous herpes virus that leads to a life-long persistence. The frequency of infection ranges from 50% to 100% in the general adult population [3]. Human cytomegalovirus causes severe and often fatal disease in immunocompromised individuals including recipients of organ transplants and AIDS patients. It routinely reactivates in healthy virus carriers, but this is usually controlled by the host immune response. Monocytes may be an important reservoir for latent HCMV; however, the primary reservoir may be a more primitive cell from the myeloid lineage. Reactivation may result from cellular differentiation or inflammation [3]. Resistance to apoptosis is a mechanism of carcinogenesis and also way for resistance to chemotherapy by cancer cells. HCMV infection was reported to protect fibroblasts from apoptosis induced by adenovirus E1A protein. Moreover, the HCMV IE1-72 and IE2-86 proteins inhibited apoptosis induced by the adenovirus E1A and TNF-α and HCMV exerts its antiapoptotic effects through IE proteins by both p53-independent and p53-dependent mechanism [4] .

Few data is available for the incidence of CMV and its clinical impact in the prognosis of AML. The aims of the present study were to assess prospectively the incidence of active CMV infection in Sudanese patients with AML and to describe the impact of CMV in prognosis of AML by the evidence of hematological prognostic markers (TWBC and blast count).

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METHODOLOGY

Study design: Analytical case control study

Ethics approval: The study was approved by the IEC and Consents were obtained from the parents/ caregivers of the subjects and controls after explaining to them, in detail, the objectives of the study as well as

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the method of specimen collection.

Study locus and period: The patients were attendants of clinics and hospital in Khartoum state, Sudan from December 2013 to September 2014.

Sample size: One hundred patients with AML and100 age and gender healthy controls were studied.

Inclusion criteria: The diagnosis was confirmed by examination of both peripheral blood and bone marrow examination. All the patients were enrolled in the study before receiving the first course of chemotherapy. The selection criteria for the patients and controls were the lack of recent blood transfusion history and taking any medication with mineral supplement.

Exclusion criteria: Any patients with known history of autoimmune diseases or immunosuppression and those in medications that affect the immune system were excluded.

Methodology: Five ml of fasting blood sample was collected from the antecubital vein of each of the case and control group. Three ml were taken in an anticoagulated tube (EDTA) the rest of the sample was taken into plain tube. Samples with signs of hemolysis were discarded. The blood was then allowed to clot and centrifuged for 15 minutes at 3000 rpm to extract the serum. The serum was aliquoted and stored at -20°C.

Full blood count (CBC): Full blood count was performed from EDTA samples within half hour after collection using automated blood cell counter (SysmexKX21) to obtain total white cell count. A microscopic examination of peripheral blood film was done to get the blast count.

Immunological Analysis: Serum was test for CMV IgG and IgM antibodies by cobas e411 using ECL technology (roche diagnostics, Germany).

Statistical Analysis: Statistical analyses were carried out using the SPSS® statistical software package (SPSS for Windows version 21.0 SPSS Inc., Chicago, Illinois, USA).

RESULTS

Out of the AML patients 85/100 (85.0%) were positive for CMV IgG while 18/100 (18%) of them were positive for CMV IgM. All the controls 100/100 (100%) were negative for CMV IgM and 17/100(17%) were positive for CMV IgG. P value in Table 1.

Table 1. The seroprevalence of CMV IgG and IgM antibodies among the case and control groups

Group	CMV IgG		CMV IgM	
	Positive	Negative	Positive	Negative
Cases	81 (81%)	19 (19%)	18 (18%)	82 (82%)
Control	17 (17%)	83(83%)	11 (11%)	100 (100%)
P value	< 0.05		>0.05	

Table 2. Comparison of TWBC and blast count between patients who positive and those who negative for CMV (IgG and IgM) antibodies

Study Group	CMV IgG		CMV IgM		P value
	Positive	Negative	Positive	Negative	
TWBC/µl	201.0 ± 78.4	96.4 ± 38.8	187.6 ± 62.5	109.8 ± 43.3	< 0.05
Blast count/µl	168.3 ± 59.8	88.7 ± 29.2	157.5 ± 55.7	100.5 ± 40.2	< 0.05

The total white cell count and blast count were significantly higher in AML patients who were positive for CMV (IgG or IgM) compared to those who were negative, P value in Table 2.

DISCUSSION

Human CMV cellular entry activates intracellular signaling pathways such as focal adhesion kinase, mitogen-activated protein kinase (MAPK), and phosphatidylinositol-3-OH kinase (PI3-K) all of which are known to play key roles in cancer progression. In addition, they played the role of HCMV gB in cell adhesion and signaling capabilities. HCMV infection is involved in cancer pathogens via modulation of apoptosis, cell migration, and angiogenesis. In fact, mixed infections with different genotypes of HCMV were detected in healthy and immunosuppressed patients, including patients undergoing lung transplant and AIDS patients. In addition, mixed genotypes infection was found to be associated with increased morbidity and mortality of solid organ transplant patients [5].

In this study we found that the seroprevlance of CMV IgG antibodies was higher in AML patients than in controls indicating an association between AML and CMV infections. High incidence of CMV in AML was found by Capria and his colloquies and AML patients with CMV infection who were not receive antiviral treatment were reported to have more hospital admissions than those who received treatment and those with higher CMV viremea had more clinical complications [6]. Early treatment of CMV infection in patients with hematologic malignancies resulted in a favorable outcome of CMV reactivation [7]. Our results also observed that AML patients with CMV infection have poor prognosis than those without CMV infection by the evidence of hematological prognosis markers considering total white cell count and blast count.

The role of HCMV in cancer etiology was recommended for investigation following the development of advanced and sensitive laboratory techniques that can detect virus genomic, protein and secretome products in cancer tissues. [3]This being due to facts that reports have shown that HCMV-DNA was detected in colorectal cancer tissues but not in normal tissues of the colon,

[8] and in carcinoma tissue of malignant glioma [9] and prostate cancer [10]. CMV is reported to have an oncogenic potential role in breast cancer [11] and to have possible causal relationship with mucoepidermoid carcinoma [12] .

CONCLUSION

CMV infections may play a role in the carcinogenesis and prognosis of AML carcinogenesis. Patients with AML should be screened and monitored for CMV as it may provide a novel target in cancer treatment.

CONFLICT OF INTEREST: We hereby declare that we conducted this research in the absence of any commercial or financial benefits.

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