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Potential oncogenic role of human cytomegalovirus in colorectal cancer

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***Abstract*---**Aims: This study was conducted to investigate whether there is to detect the oncopotenial role of HCMV in colorectal cancer (CRC). Material and methods: 30 samples of formalin fixed-Paraffin embedded archival tissues were collected from patient suffering of CRC , In addition to 10 samples of free cancer tissue for determine of expression CMV by using immunohistochemistry. Results: There is no expression of CMV in all samples of CRC and control groups. Conclusion: Althought the several research findings that support HCMV oncomodulatory role in CRC , there is no correlation of the CMV infection and CRC as a pro-tumorigenic factor in the current study.

***Keywords*---**CMV, CRC, pp65, IHC, oncogenesis.

Introduction

The fourth most common cause of cancer death in both men and women, colorectal cancer is the third most common cancer in the world. Each year, more than 1.36 million new cases of the disease are identified worldwide, and more than 600,000 people pass away from it [1,2]. According to the latest WHO data published in 2018, the expected mortality in Iraq due to CRC cancer was 6.30%. while The death rate for colorectal cancer in some Arab countries recorded (13.92% Jordan, 14.88 %Syria, 4.23% Egypt, 5.64 %Oman, 7.14 %Saudi Arabia and 8.14% Qatar) [3]. Incidence of CRC are rising due to lifestyle and aging-related factors. However, a small number of CRC cases may be due to an underlying genetic disease, and the disease has a variable etiology that includes genetic and environmental factors as well as inflammatory bowel disease [4]. There are potential for early detection and prevention because the formation of CRC is a multi-step process that frequently takes place over a period of more than 10 years [5].

The viral pp65 structural antigen and it is important component of HCMV tegument because of its different roles in different enents of the virus replication cycle [6,7] .Kalejta illustrated that during viral infections ,pp65 rescind both arms of immunity (innate and adaptive) and so evade the human immune response to the infection [7] Although the virus not generally not considered as oncogenic, HCMV infection has been recorded in several malignant diseases. Some studies use the phrase of “oncomodulation” to explaine the role of HCMV in cancer pathology which means that tumor cells are infected with viral particles that leading to increases the burden of their malignancy[8,9].

Despite not being a fully acknowledged oncogenic virus. [10]. Although CMV is widespread in the community, it is more significant when there is immune suppression during pregnancy [11]. Asymptomatic hosts distribute CMV through a variety of bodily fluids, including saliva ,urine and vaginal secretions [12]. Although there isn't as much epidemiological evidence linking CMV infection to CRC, There is epidemiologic and genetic proof that CMV causes ovarian, breast,

and medulloblastoma tumors, among other malignancies [13]. CMV has however been discovered in CRC sections. Seven colon cancers from an early research were found to have CMV in 57 percent of them [14]. The goal of this study was to see if there to determine expression of CMV in terms of developing latent infections, if CMV can enhance oncogenesis.

Materials and Methods

Immunohistochemisty assay of CMVpp65 expression

30 samples of formalin fixed-Paraffin embedded were collected from patient suffering of CRC (18 male and 12 female) randomly from the pathological records kept at the Gastrointestinal and liver teaching Hospital in Baghdad between between January 2020 to October 2021. One pathologist evaluated the CRC samples to identify the grade of CRC. Each block was 4 mm thick when cut, and it was adhered to positively charged slides. To be used for hematoxylin and eosin staining, the first tissue section was mounted on a standard slide. Additionally, other sections were stained with anti-CMVpp65 antibodies from the United Kingdom's ABCAM firm on charged slides for immunohistochemistry. as per the manufacturer's guidelines [15].

Determine of Immunohistochemistry finding

Immunostaining on CRC tissue that is absent indicates a negative reading, while cells that have brown cytoplasmic pigmentation indicate a positive reading. By employing a light microscope and a scoring system that took into account both the strength of the antibody and the frequency of positive cells.The absence of the expression in all samples support the null hypothesis
[16].

Results and Discussions

30 samples (18 males and 12 females) were collected from patients with CRC with grade G2 and their ages ranged from (22 to 79) year, with an average of 55.5 year. All of them had tumor adjacent normal (TAN) samples that matched. the research investigation of CMV infection showed no evidence of oncogenic activity. There is no expression of CMV in all samples of CRC and control groups (Table 1, Fig. 1).

Table 1
Immunohistochemistry expression CMV

	CMV No. (%)	Control Group
Positive	0 (0.00%)	0 (0.00%)
Negative	30 (100%)	10 (100%)
Total	30	10

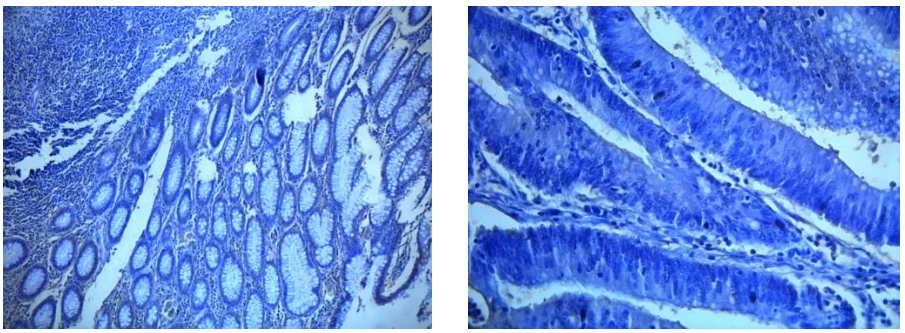

Figure 1. Immunohistochemical results in Colorectal Carcinoma tissues. left (10x) , right (40X) :Negative expression of CMV in Colerectal carcinoma

CRC it is considered one of the most common causes of tumor and Patients with CRC the prognosis is greatly determined by their diagnosis stage. As a result, early detection is crucial for boosting survival time [17].

Many research about the investigation of CMV expression in CRC and the link between CMV infection and human cancers is becoming increasingly clear althought, the current paper found that there is no relationship between CMV infection and CRC. this study in agreement with another study that proved there isn't as much epidemiological evidence linking CMV infection to CRC [13] this may attributed to how much the virus can escape from the monitoring of the individuals immune components by to create an environment highly suppressive around the tumor [9].

Furthermore in this regard, Several studies focused on the non-specific immune molecules that are designed as sensors for a broad spectrum of viral and bacterial pathogens known as pattern recognition receptors (PRRs) may eliminate the viral infection [18].

Other cancers, such as breast, medulloblastoma, and ovarian cancer, have epidemiological and molecular evidence of CMV oncogenic activity [11]. This study agrees with another study that found no CMV in 65 colorectal adenomas and 65 colorectal adenocarcinomas using immunohistochemistry [18].while According to meta-analysis, CMV infection is linked to a 6.6 % chance of having CRC [19]. Possible explanations for this result include the fact that formalin processing can make it difficult to detect CMV within tissues, so PCR is a more sensitive method for determining prevalence [20] . CMV DNA was detected in 11 % of the 56 formalin-fixed paraffin-embedded CRC by PCR [21]. A characteristic that implies the interaction between CMV and host cells derived from the intestine is still unknown, which could affect viral detection [10].

Conclusion

We found that there is no link between CMV infection and CRC as a pro-tumorigenic factor, we suggest using of supplementary markers to known histopathological diagnostsic components; which could potentially be used in prognosis and targeted therapy. Further investigations with larger samples and other molecular tools is recommended to highlight the role of the virus.

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