

Could JC virus provoke metastasis in colon cancer?

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virus (JC virus) in a small cohort of patients with colon cancer and to assess its presence in hepatic metastasis.

METHODS: Nineteen consecutive patients with histologically diagnosed colon cancer were included in our study, together with ten subjects affected by histologically and serologically diagnosed hepatitis C virus infection. In the patients included in the colon cancer group, JC virus was searched for in the surgical specimen; in the control group, JC virus was searched for in the hepatic biopsy. The difference in the prevalence of JC virus in the hepatic biopsy between the two groups was assessed through the χ^2 test.

RESULTS: Four out of 19 patients with colon cancer had a positive polymerase chain reaction (PCR) test for JC virus, and four had liver metastasis. Among the patients with liver metastasis, three out of four had a positive PCR test for JC virus in the surgical specimen and in the liver biopsy; the only patient with liver metastasis with a negative test for JC virus also presented a negative test for JC virus in the surgical specimen. In the control group of patients with hepatitis C infection, none of the ten patients presented JC virus infection in the hepatic biopsy. The difference between the two groups regarding JC virus infection was statistically significant ($\chi^2 = 9.55, P = 0.002$).

CONCLUSION: JC virus may play a broader role than previously thought, and may be mechanistically involved in the late stages of these tumors.

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Key words: John Cunningham virus; Colon cancer; Metastasis

Core tip: This is the first case-control study, to our knowledge, assessing, although with a small sample size, the potential metastatic spread of John Cunn-

Abstract

AIM: To evaluate the prevalence of John Cunningham

ham virus associated with colon cancer.

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INTRODUCTION

Colorectal cancer (CRC) is the third most frequent malignancy, and constitutes the second leading cause of cancer mortality among both men and women in the United States^[1]. Mortality in CRC is usually caused by metastatic disease. Even if increasing efforts to the diagnosis of CRC at an early stage with screening programs, more than 25% of patients are still diagnosed with metastatic disease, and a further 25% develop metastases. Up to now, the molecular mechanisms underlying the development of metastasis are not fully understood^[2]. Actually, infectious diseases are acquiring relevance because they are thought as leading pathogenic elements in human cancer: in fact all about twenty percent of human cancers are associated with infectious agents, particularly in the gastrointestinal tract^[3], but this is not a mainstream oncologic research area. It has been thought that the development of several types of human cancers could be triggered by exposure to different infectious agents, such as human papilloma virus (HPV) infection associated with cervical carcinoma^[4], hepatitis B virus associated with liver carcinoma^[5], Epstein-Barr virus associated with Burkitt lymphomas^[6], HTVL-1 associated with Adult T-cell Leukemia/Lymphoma^[7], or Helicobacter pylori associated with gastric carcinoma^[8]; more recently a human retrovirus, XMRV, has been associated with sporadic prostate cancer^[9-11]. In addition, an association has been reported between the development of lower gastrointestinal tract neoplasias and infectious agents^[8], *e.g.*, between CRC and John Cunningham virus (JC virus) infection.

JC virus, a member of the polyomaviridae family, ubiquitously infects humans, 70% to 80% of the adult population having JC virus-specific antibodies^[12,13]. Several studies demonstrated that JC virus infection takes place during early childhood and remains subclinical. After primary infection, JC virus can be found in the kidneys, B lymphocytes, and gut mucosa.

However, under conditions of severe immunosuppression, the virus could become reactivated and induce the fatal demyelinating disease progressive multifocal leukoencephalopathy (PML)^[14]. In addition, there is an increasing evidence that JC virus may be associated with several human neoplasias. In fact, JC virus genomic sequences and oncogenic T-antigen (T-Ag) expression have been reported in a variety of human malignancies,

including brain tumors^[15,16] CRC^[17-20], gastric cancer^[21], and esophageal cancer^[22].

JC virus has been reported to be associated with CRC and could contribute to the cancer phenotype by several mechanisms. Among JC virus proteins, two in particular, large T-antigen and agnoprotein, could interfere with cell cycle control and genomic instability mechanisms, but further viral proteins could also contribute to cell transformation. Some viral DNA sequences are found in carcinoma lesions, but less frequently in adenomas, and not in the normal tissue. These findings suggest that viral DNA integration in the host cell genome might result in chromosomal damage and malignant transformation^[23]. However, to date its role in provoking metastasis has not been demonstrated, though it has been hypothesized that JC virus T-Ag could mediate metastasis in CRC cells through increased migration and invasion^[24].

The aim of this study is to evaluate the prevalence of JC virus in a small cohort of patient with colon cancer and to assess its presence in hepatic metastasis, comparing it with a cohort of patients with liver disease but without colon cancer.

MATERIALS AND METHODS

Study population

Nineteen consecutive patients (47.4% male, 52.6% female) with histologically diagnosed colon cancer, followed between January 2012 and October 2012 at our hospital, were included in the study, together with ten subjects, employed as a control group of individuals in the same geographic areas, affected by histologically and serologically diagnosed hepatitis C virus infection. This cohort of control subject was chosen to assess the prevalence of JC virus in the livers of patients without known primary colorectal cancer.

Among patients from the colon cancer group, JC virus was searched for in the surgical specimen (primary colon cancer tissue and liver metastasis tissue); in the control group, JC virus was searched for in the hepatic biopsy. Liver biopsies were all standard percutaneous samples, and the threshold of adequacy for histological assessment was the presence of more than five portal tracts.

The difference in the prevalence of JC virus in the hepatic biopsy between the two groups was assessed through the χ^2 test.

DNA extraction

Paraffin-embedded tissues were sectioned at 10 microns and five sections were cut with a standard microtome and transferred into a 1.5 mL microtube.

To prevent cross-contamination between the samples, the microtome blade was washed with xylene and ethanol after sectioning of each block.

Genomic DNA was extracted from paraffin embedded tissue section using the ZR Genomic DNA-Tissue Miniprep (Zymo Research, United States), according to the manufacturer's recommendations.

Table 1 Clinical and pathological features of the patients with colorectal cancer

Age (median, range), yr	70 (59-87)
Location of the colorectal cancer (<i>n</i>)	Caecum and ascending colon: 12/19 Transverse colon: 1/19 Descending colon: 2/19 Sigma 3/19 Rectum 1/19
Sex (Male:Female)	7:12
Grading	G1: 1/19 G2: 12/19 G3: 6/19
Staging according to Dukes' Classification (<i>n</i>)	A: 0/19 B1: 0/19 B2: 2/19 C1: 3/19 C2: 10/19 D: 4/19
Mucinous component (<i>n</i>)	5:19
Signet ring component (<i>n</i>)	5:19
Presence of tumor infiltrating lymphocytes (<i>n</i>)	12:19
Perineural invasion (<i>n</i>)	10:19
Microvascular invasion (<i>n</i>)	10:19
Lymphangiosis (<i>n</i>)	1:19
JC virus positivity in the colonic specimen (<i>n</i>)	4:19
Liver metastasis (<i>n</i>)	4:19
JC virus positivity in the hepatic specimen (<i>n</i>)	3:19

JC virus: John Cunningham virus.

Extreme caution was taken to perform all preparatory polymerase chain reaction (PCR) steps, including DNA extraction in a separate room isolated from any post-PCR samples to prevent contamination.

All the DNA samples were amplified using beta-globin primers (fragment of 175 bp) to confirm their integrity.

Nested PCR for the JC virus genome

For the detection of JC virus gene sequences, polymerase chain reaction amplifications were performed using gene-specific primers for T-antigen.

For JC virus T-antigen, T1 and T2 (nucleotides 3049-3069 of the Mad-1 strain, 5' TGGCCTGTA-AAGTTCTAGGCA 3' and 3229-3207, 5' GCAGAGT-CAAGGGATTTACCTTC 3' respectively) which amplify sequences in the NH2-terminal region of the JC virus T-antigen, were used for the first PCR, whereas T1 and T3 (nucleotides 3193-3171, 5' AGCAACCTTGATTGCITTA-AGAGA 3') were used for the second PCR (110 bp)^[25].

PCR reaction mixture contained 0.5 U Taq polymerase, 1 × PCR Buffer (50 mmol/L KCl and 10 nmol/L MgCl₂, 10 pmol of each dNTPs, 1.5 mmol/L MgCl₂, 10 pmol of each primers and 100-200 ng of extracted DNA.

PCR conditions were denatured at 95 °C for 10 min, followed by 30 cycles of denaturation at 95 °C for 15 s, annealing at 55 °C for 30 s and extension at 72 °C for 30 s followed by 7 min final extension at 72 °C.

Nested PCR was carried out as the first PCR cycles, using 1% (volume) of the first PCR product with internal primers.

The PCR amplification products were run on 2%

agarose gel and stained with ethidium bromide and visualized under ultraviolet light.

RESULTS

Clinical and demographical data of the study population are summarized in Table 1.

Four out of 19 patients (21.05%) with colon cancer had a positive PCR test for JC virus, and four (21.05%) had liver metastasis. Among the four patients with liver metastasis, three out of 4 (75%) had a positive PCR test for JC virus both in the surgical specimen and in the liver specimen; the only patient with liver metastasis with a negative test for JC virus also presented a negative test for JC virus in the primary tumor.

In the control group of patients with hepatitis C infection, none of the ten patients (0%) presented JC virus infection in the hepatic biopsy.

The difference between the two groups regarding JC virus infection was statistically significant ($\chi^2 = 9.55$, $P = 0.002$).

DISCUSSION

JC virus DNA sequences and proteins have been found in a wide range of human neoplasias of glial and non-glial origin, as gliomas, ependymomas and medulloblastomas, as well as in several non-neural clinical specimens of gastrointestinal tumors, such as CRC^[8], suggesting that they could infect a broad range of cell types. However, the role of JC virus in such neoplasias is poorly understood.

Even if several studies have evaluated the role of the presence of JC virus DNA in colonic tissue using PCR, more recently Burnett-Hartman and coworkers reviewed five studies examining colorectal neoplastic tissue detecting JC virus DNA in colorectal neoplasias at varying frequencies, finding from 26% to 89% of carcinomas positive for JC virus.

A very important challenge is to establish whether the presence of JC virus presents any difference between tumors of different grades and its normal surrounding mucosa. Few studies have been performed in this context.

Two studies evaluated colorectal adenomatous tissue from separate patients with adenomas and normal colorectal tissues from controls. The first study reported a JC virus infection in 61% of cancerous tissue, 60% of adenomatous tissue and 30% of normal tissue samples from controls, showing a OR = 6.2 (95%CI: 2.4-16.6) comparing neoplastic tissue to normal tissue. This study showed that JC virus viral copy numbers were statistically significantly higher in neoplastic colorectal tissue with regard to normal colorectal tissue^[26]. The second study presented lower rates of detection for JC virus, finding 26% of cancerous colorectal tissue, 5% of adenomas and 0% of normal tissue positive for JC virus^[27].

Furthermore, in the study performed by Link and coworkers^[24], some phenotypic changes were demonstrated that were associated with marked alterations in the expression of a large number of genes of JC virus. These results are in line with a previous study by Nerurkar and colleagues in which the authors analyzed gene expression alterations following transfection of a full-length JC virus plasmid into glial cells^[28]. Indeed, the study of Link and coworkers suggests a novel role for JC virus T-Ag in human CRC. The authors demonstrated that transfection of JC virus early transcripts into cancer cells could increase migration and invasion through up-regulation of metastasis-associated genes^[24].

Our study presents some limitations, like the retrospective design, the small number of patients with liver metastasis and the absence of detection of JC virus in the normal mucosa surrounding the colorectal cancer, as well as the absence of mention of the level of viral expression in the analyzed tissue. However, the primary aim of our study was simply to assess the presence of JC virus in the hepatic metastasis of colorectal cancer, comparing it with a cohort of patients with liver disease but without colon cancer. Furthermore, our points of strength are the presence of a control group and the finding of a prevalence of JC virus, in colon cancer, which has largely been overlooked in the scientific literature, with the finding of the scientific literature, with the exception of the study performed by Link and co-workers^[24].

Based on this data, we propose that JC virus T-Ag may play a broader role than previously thought, and may be mechanistically involved in the late stages of these tumors.

Forthcomings prospective case-control studies, with a larger number of patients in both the arms and targeted to evaluate the difference in the level of expression of

JC virus in the primary tumoral colonic tissue and in the normal surrounding colonic mucosa, as well as to study migration and invasion, could clarify the true prevalence of JC virus in colon cancer and in liver metastasis, making it possible to find a true “mechanical” role of JC virus in the late stages of CRC.

COMMENTS

Background

Infectious diseases are acquiring relevance as important pathogenic elements in human cancer, since almost one fifth of human cancers are associated with infectious agents, particularly in the gastrointestinal tract. An association has recently been reported between colorectal cancer and John Cunningham virus (JC virus) infection.

Research frontiers

Up to date, the role of JC virus in provoking metastasis has not been demonstrated, though it has been hypothesized that JC virus T-Ag may mediate metastasis in colorectal cancer (CRC) cells through increased migration and invasion.

Innovations and breakthroughs

Recent reports have demonstrated that transfection of JC virus early transcripts into cancer cells could increase migration and invasion through up-regulation of metastasis-associated genes. Increased expression of phosphorylated AKT and ERK1/2 and the reversible effect of PI3K/AKT and MAPK pathway inhibitors imply, at least in part, the involvement of PI3K/AKT and MAPK pathways. Detection of JC virus T-Ag expression in primary CRCs and their metastases suggests a novel role for JC virus T-Ag in metastasis during the late stages of CRC.

Applications

This is the first case-control study, to our knowledge, assessing, although with a small sample size, the potential metastatic spreading of JC-virus associated colon cancer.

Terminology

JC virus, a member of the polyomaviridae family, ubiquitously infects humans, 70% to 80% of the adult population having JC virus-specific antibodies. Epidemiological studies have demonstrated that JC virus infection takes place during early childhood and usually remains subclinical. JC virus has been associated with colorectal cancer and might contribute to the cancer phenotype by several mechanisms. Among JC virus proteins, two in particular, large T-antigen and agnoprotein, can interfere with cell cycle control and genomic instability mechanisms, but other viral proteins might also contribute to cell transformation.

Peer review

Authors are presenting preliminary data on an interesting association, JC virus and colon cancer. Their results of 4/19 patients with colorectal cancer having polymerase chain reaction evidence of JC virus infection are supportive of this association and are therefore worthy of publication.

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