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Research Article

Investigating Epstein-Barr Virus IgG Antibodies Emphasizing Single Nucleotide Polymorphisms as a Biomarker for Oncogenesis and Immune Evasion in Lung Cancer among Iraqi Patients

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Abstract

Background: Lung cancer is the predominant cause of cancer-related mortality globally, representing 18.4% of all cancer deaths. The economic and social impact of the disease is substantial for patients and their families. The Epstein-Barr virus, discovered in 1964, is a significant oncogenic virus accountable for approximately 200,000 cancer cases per year and 1.8% of worldwide cancer-related fatalities. The Kirsten rat sarcoma virus gene, part of the RAS oncogene family, was first identified in lung cancer in 1982 on chromosome 12 (12p11.1–12p12.1).

Objectives: To investigate the intricate molecular relationships between EBV immunoglobulin G (IgG) Sero-positivity, KRAS mutation-induced immunogenicity, and the genetic polymorphism rs121913238, attempting to examine the role of these factors on oncogenic signaling pathways, immune evasion, modifications in the tumor microenvironment, and their collective effect on the development and progression of lung cancer.

Methods: Between November 2023 and August 2024. A case-control study was executed at two oncology institutions in Iraq: Al-Amal National Hospital for Oncology in Baghdad and the Euphrates Center for Cancerous Tumors in Najaf. A total of 50 patients diagnosed with lung cancer, validated by histological examination. These individuals had not undergone previous radiotherapy or surgery, although some had commenced chemotherapy. For comparative purposes, 50 healthy individuals were enlisted from the University of Baghdad (25 smokers and 25 non-smokers). Anti-EBV IgG concentrations were quantified via ELISA, succeeded by molecular analysis employing conventional polymerase chain reaction (PCR) and Sanger sequencing to identify single nucleotide polymorphisms (SNPs) in 30 blood samples, 15 from lung carcinoma patients and 15 from healthy individuals, based on the ELISA results. The remaining samples were excluded from the polymorphism analysis and had modest antibody concentrations, assumed to lack a substantial effect.

Results: EBV IgG levels were markedly increased in patients relative to controls. Indicating a possible association with lung cancer. The specific SNP (rs121913238) remained undetected; yet, an alternative SNP (rs11836509) was identified in 8 samples (6 patients, 2 controls).

Conclusion: While no direct correlation was shown between EBV and KRAS mutations, EBV infection is associated with lung cancer, and rs11836509 may contribute to disease development. Additional research is necessary to clarify these links.

Keywords: Epstein-Barr virus; Kirsten rat sarcoma virus; Lung cancer; Mutation; Polymorphism

Introduction

Cancer remains a significant global health concern, despite advancements in diagnostic and therapeutic techniques (1). It is a complex array of carcinogenic diseases capable of metastasizing or invading other regions of the body. It progresses through a multi-stage procedure(2). Lung cancer is the most common type of cancer and considered the primary cause of cancer-related mortality globally. Nonetheless, the incidence and mortality rates of lung cancer vary significantly worldwide, indicative of diverse patterns of tobacco use, environmental risk factor exposure, and genetic predispositions (3).

The delayed identification of this cancer significantly contributes to advanced-stage diagnoses and unfavorable outcomes (4). Malignancies originating from different organs may metastasize to the lungs(5). This cancer is divided into two major groups, Small-Cell Lung Cancer (SCLC) and Non-Small-Cell Lung Cancer (NSCLC), which are further classified into: Squamous cell carcinoma, large-cell carcinoma, and adenocarcinoma (6). Between 15–20% of lung cancer patients have small cell lung cancer (SCLC), and the rest 80–85% have non-small cell lung cancer (NSCLC) (7). Mutations affecting proto-oncogenes and tumor suppressors, along with the emergence of host immunological dysregulation, are the root causes of the genetic and epigenetic abnormalities that propel lung cancer (8). Lung cancer generally has a five-year survival rate of less

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than 20% (9). The postoperative 5-year survival rate for micro-invasive carcinoma and carcinoma in patients with early-stage lung cancer was about 100% (10). The 5-year relative survival rate for all lung cancers (NSCLC and SCLC combined) is 19%, and it is higher for NSCLC (23%) than for SCLC (6%).

Annually, over 1.4 million malignancies generated by viruses are diagnosed, accounting for about 10% of the global cancer burden, with over 85% occurring in lower- and middle-income countries. The viruses linked to the highest incidence of cancer include human papillomaviruses (HPVs) responsible for cervical cancer and various other epithelial malignancies, and hepatitis viruses HBV and HCV, which account for the predominant occurrences of hepatocellular carcinoma. Additional oncoviruses comprise Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), human T-cell leukemia virus (HTLV-I), and Merkel cell polyomavirus (MCPyV)(11). The Epstein-Barr virus (EBV) is a prevalent, carcinogenic virus linked to several human cancers and autoimmune diseases (12).

EBV belongs to the subfamily Gamma herpesvirinae of Lymphocryptovirus, which is an enveloped gamma herpesvirus, it is a double-stranded DNA virus linked to the onset of several malignancies, including lymphoma, nasopharyngeal carcinoma, and gastric cancer(13), invasive ductal carcinoma (IDC) of the breast, where it correlates with the overexpression of latent membrane protein 1 (LMP1)(14), and Hodgkin's lymphoma (HL) exhibits genetic changes, including amplifications of chromosome 2p and JAK2 (15).

EBV is the first recognized human oncogenic virus, responsible for approximately 200,000 cancer cases and about 1.8% of annual cancer-related fatalities. In the last four decades, accumulating data has substantiated a significant link between EBV infection and a specific fraction of lung cancers (16). The infectious virions are primarily distributed through saliva interchange, although body fluids like blood or urine can convey them. Like most human herpesviruses, vaccine-mediated inhibition of EBV infection is still in the research and development stage and is not a possibility, except for varicella-zoster virus (VZV). It is estimated that around 90% of adult people worldwide are currently infected with EBV(17). According to one theory, EBV might first reach the oral cavity's replication-permissive epithelial cells, where it would then initiate active lytic replication. EBV infects B lymphocytes and epithelial cells of the immune system; the initial epithelial cells subsequently release infectious virions that infect adjacent penetrating B cells, which produce the whole spectrum of viral latency transcripts, referred to as type III latency. The alternate concept posits that EBV infects B cells following its passage through polarized human oral epithelial cells via apical to basolateral transcytosis, without inducing lytic replication(18).

The KRAS gene is part of the rat sarcoma viral oncogene (RAS) family, which also encompasses the human Harvey and neuroblastoma rat sarcoma viral oncogenes (HRAS, NRAS) isoforms(19), and is the most frequently mutated RAS isoform. KRAS constitutes 85% of RAS mutations detected in human malignancies and is seen in 35% of lung adenocarcinomas (LUADs) (20). In 1982, the KRAS was identified in lung cancer located on the short arm of chromosome 12 (12p11.1–12p12.1) (21). About 80% of cancers linked to the RAS gene are caused by KRAS mutations, which are the most prevalent form of RAS mutation(22). KRAS mutations are dominated by single-base missense mutations, 98% of which are found at codon 12 (G12), codon 13 (G13), or codon 61 (Q61) (23).

Lung cancer biomarkers are essential for the early diagnosis, prognosis, and individualized treatment of lung cancer, especially NSCLC. Their identification and deployment have markedly enhanced lung cancer management, facilitating tailored therapy and improving patient outcomes. Frequently evaluated biomarkers, including EGFR, ALK, and ROS1, are crucial for directing targeted therapies (24), whereas IHC assays for proteins like PD-L1 and Ki-67 facilitate the evaluation of tumor attributes and forecast responses to immunotherapy (25). Moreover, biomarkers are progressively acknowledged for utility in lung cancer screening, facilitating risk classification and minimizing superfluous therapies (26). Nonetheless, additional validation is required to incorporate these biomarkers into standard screening techniques successfully.

The study aimedd to analyze the complex molecular interactions among EBV IgG seropositivity, KRAS mutation-induced immunogenicity, and the genetic polymorphism rs121913238, emphasizing their combined effects on driving oncogenic signaling pathways, evading immune surveillance, and altering the tumor microenvironment to promote lung cancer initiation, progression, and phenotypic diversity.

Patients and Methods

From November 2023 to August 2024, fifty lung cancer patients were recruited from Al-Amal National Hospital for Oncology in Baghdad, Iraq, and the Euphrates Center for Cancerous Tumors in Najaf, Iraq. Additionally, fifty healthy individuals (25 smokers and 25 nonsmokers) from the University of Baghdad served as the control group. All the healthy individuals were evaluated with a health questionnaire and chosen based on not having been previously diagnosed with lung cancer, all with no previous cancer history. Blood samples were obtained using venipuncture, with 5 mL allocated into two segments: Serum and whole blood. The serum was utilized to identify anti-EBV antibodies, whilst the whole blood was employed for DNA extraction and identifying KRAS single nucleotide polymorphisms. For DNA extraction, 2 mL of blood in EDTA tubes were processed one to three weeks after collection, while serum was obtained from 3 mL of blood in clot activator tubes, allowed to coagulate for 30 minutes, centrifuged for 10 minutes at 4000 rpm, and stored at -20°C. Anti-EBV IgG was identified in serum

utilizing the ELISA method with kit from SunLong/China Catalog Number: SL0674Hu_1. Molecular detection entailed the extraction of DNA utilizing a spin column kit (China/ Catalog Number: D1800) and the amplification of the KRAS gene (rs121913238) via conventional PCR with specific primers that we have designed (forward primer: 5'-TCCACTGCTCTAATCCCCCA-3' / reverse primer: 5'-CCCACCAGCAATGCACAAAG-3'). The cycling technique included an initial denaturation at 95°C, succeeded by 35 cycles of denaturation (95°C for 15 seconds), annealing (58°C for 30 seconds), and extension (72°C for one minute), culminating in a final extension at 72°C for 5 minutes. Amplification was verified via 0.5–1.5% agarose gel electrophoresis, and the DNA was purified using a GenepHlow™ Gel Extraction Kit (Taiwan/ catalog number: DFG100) before sequencing. Sanger sequencing of PCR amplicons was conducted on an ABI 3730xl automated sequencer at Macrogen Corporation, South Korea, and the sequencing results were processed with Geneious software to identify KRAS single nucleotide polymorphisms (rs121913238).

Ethical Approval: This study was approved by the ethical committee in the University of Baghdad, College of Science, Department of Biology, Reference No. CSEC/0222/0007) on (29/ 10/ 2023) and by the Ministry of Health/ Iraq.

Statistical Analysis: The Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted to assess the normality of the data distribution. Categorical data were expressed as counts and percentages, whilst nonparametric variables were denoted by median and interquartile range (IQR). The Kruskal-Wallis H test and the Mann-Whitney U test were employed to assess substantial variations among the medians of the research groups. One-way ANOVA and two-way ANOVA, supplemented by Tukey's test for post hoc analysis, were utilized to assess the significant differences among the means of the study groups. Receiver operating characteristic (ROC) analysis was performed to ascertain the area under the curve (AUC), 95% confidence interval (CI), cut-off value, sensitivity, and specificity. The likelihood ratio was utilized to enhance the cut-off value. Differences were considered significant when the P value was less than or equal to 0.05. The statistical analysis was conducted with GraphPad Prism 9.5 (27). The Hardy-Weinberg equilibrium analysis was used to predict the distribution of genotypes and for the calculation of allele frequencies.

Results

The levels of anti-EBV IgG antibodies were markedly elevated in lung cancer patients relative to healthy controls ($p = 0.003$), exhibiting a mean concentration of 15.0±10.2 in patients, and a mean of 11.5±1.5 in controls. The median values were 12.5 for patients and 8.9 for controls, with interquartile ranges (IQR) of 4.88 and 3.51, respectively, signifying increased variability in the control group.

When analyzed by gender within each cohort, female patients demonstrated elevated EBV IgG concentrations relative to female controls (mean 15.5 ± 11.2 vs. 12.0 ± 8.2), whereas male patients displayed greater levels than male controls (mean 14.6 ± 9.5 vs. 11.0 ± 9.2). These intra-gender comparisons substantiate the correlation between heightened EBV IgG levels and lung cancer status, while mitigating any confounding factors arising from inter-gender comparisons.

Significant disparities in smoking status were noted between smoking patients and controls ($p = 0.02$). The mean for smoking patients were 14.3±8.7, and for non-smoking patients, it was 11.4±8.2.

The examination of chemotherapeutic response revealed no substantial difference. Patients taking chemotherapy exhibited a mean anti-EBV IgG level of 14.6±9.5, whereas those not having chemotherapy had a mean of 18.0±15.0 (Figure 1).

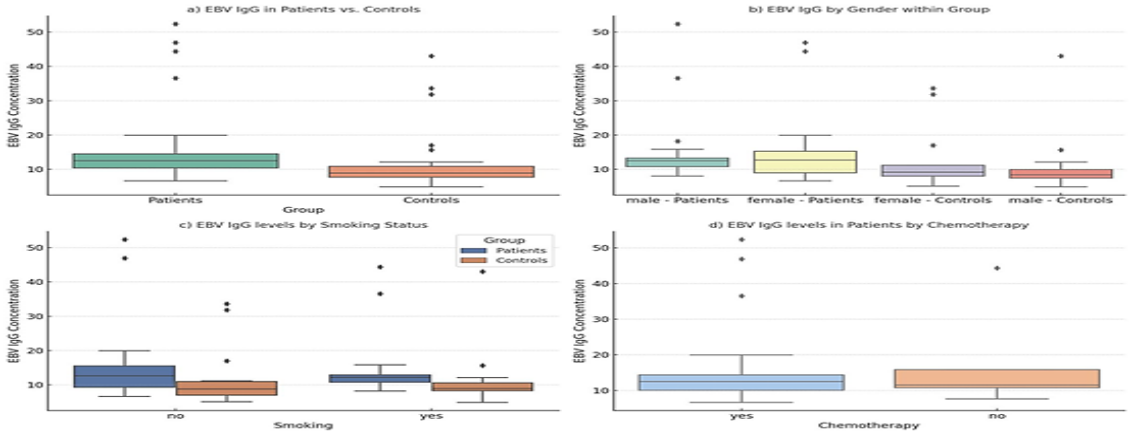

Figure 1: EBV IgG concentration in lung carcinoma patients and healthy controls

(a) Comparison of EBV IgG concentration between patients and controls
(b) EBV IgG levels stratified by gender in both patients and controls
(c) EBV IgG levels based on smoking status
(d) EBV IgG concentration in patients stratified by chemotherapy treatment
Data are presented as box plots showing median and interquartile ranges

The diagnostic efficacy of EBV levels in distinguishing patients from controls was assessed by Receiver Operating Characteristic (ROC) curve analysis. The area under the curve (AUC) was 0.7397 (95% CI: 0.6199–0.8595, p = 0.0004), signifying a moderate to strong discriminatory capacity of EBV as a prospective biomarker. The ideal cut-off value for EBV was 11.35, resulting in a sensitivity of 63.64% and a specificity of 81.25%.

The findings indicate that increased EBV levels are highly correlated with the disease and may function as a valuable diagnostic marker. Nonetheless, additional validation in bigger cohorts is necessary to ascertain its clinical utility (Figure 2).

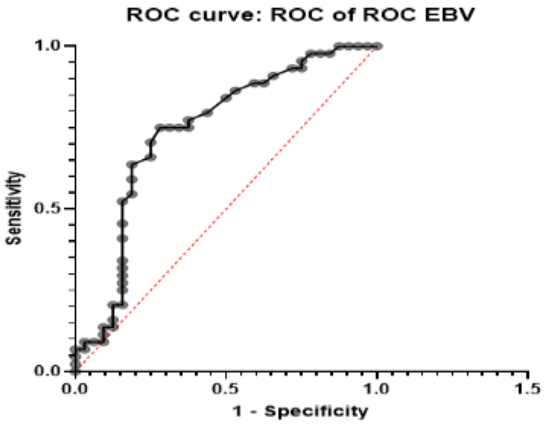

Figure 2: ROC curve of EBV IgG antibody in the samples collected from lung carcinoma patients and healthy controls

Furthermore, SNP analysis of the KRAS gene at position 915 with traditional PCR demonstrated that all samples were homozygous for the G allele (genotype GG), signifying the absence of variation at this location, (Figure 3).

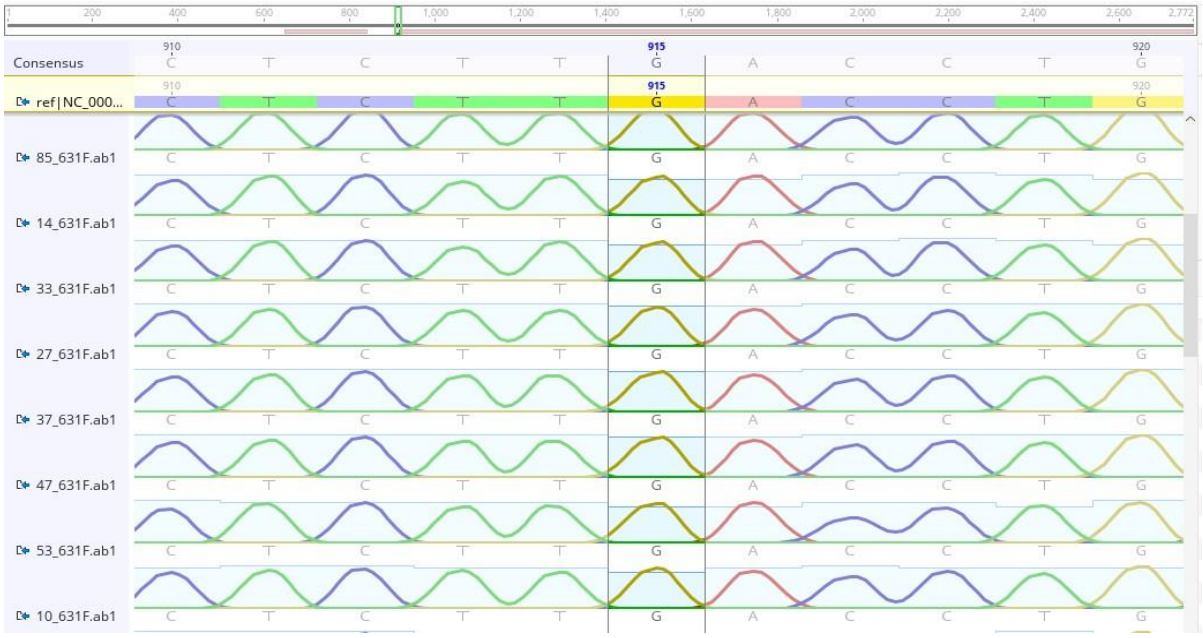

Figure 3: Examination of the SNP rs121913238 within the KRAS gene by Sanger sequencing. A solitary "G" peak signifies a G homozygous allele. All samples exhibited homozygosity for the GG genotype.

However, an unanticipated SNP at position 709 (rs11836509) was detected in 8 samples (6 patients and 2 controls) (Figure 4). The genotype ratio for -709 G/G was 60% in patients and 86.6% in controls, whereas T/G and T/T genotypes were more prevalent in patients (20% each) than in controls (6.6% each). The G allele frequency was 0.7 in patients and 0.9 in controls, whereas the T allele frequency was 0.3 in patients and 0.1 in controls, indicating a greater prevalence of the -709 T allele in patients.

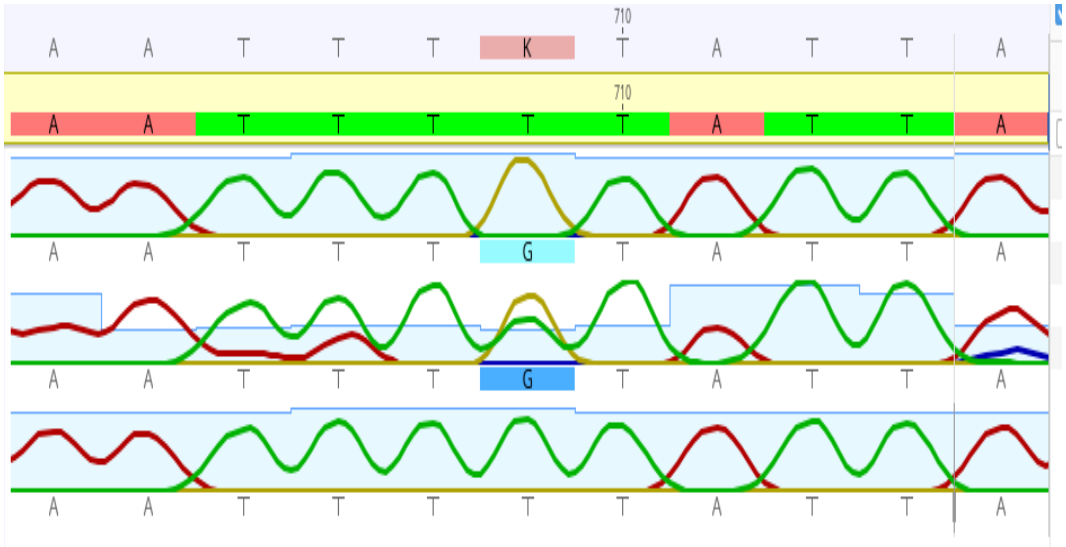

Figure 4: Examination of the SNP rs11836509 within the KRAS gene by Sanger sequencing. A solitary "G" peak signifies a G homozygous allele. A solitary "T" peak signifies a T homozygous allele. The existence of the "G" and "T" peaks signifies the G/T heterozygous allele, also referred to as K.

Discussion

This study examined the significance of SNP rs121913238 in lung cancer, and it was not present in any of the tested samples. However, SNP rs11836509 was identified in 8 samples (6 patients and 2 controls) exhibiting this SNP. This finding indicates a possible association between SNP rs11836509 and susceptibility to lung cancer. This aligns with the findings of Khono et al. (28) in Japan and Antontseva et al. (29) in Russia, which confirms its association with lung carcinoma. This finding substantiates the concept that SNP rs11836509 may influence genetic predisposition to lung cancer, necessitating additional investigation into its functional role.

The elevated EBV IgG levels in patients relative to controls in this investigation supports the notion that chronic EBV reactivation contributes to oncogenesis through pathways including inflammation, immunosuppression, and genomic instability (30). Increased EBV IgG levels are commonly noted in malignancies, autoimmune illnesses, and chronic inflammatory conditions as a result of an immunological response (31). Despite higher EBV IgG levels in patients relative to controls, no direct correlation was identified between EBV IgG and KRAS IgG levels. The absence of such a correlation indicates that although viral reactivation may significantly influence immune regulation and cancer progression, it seemingly does not directly interact with specific genetic abnormalities such as KRAS. The interplay between viral reactivation and genetic predisposition (e.g., SNP rs11836509) may provide a synergistic impact that promotes lung cancer growth. The integration of EBV IgG and SNP data provides substantial insights into the etiology of lung cancer. Increased EBV IgG levels suggests a vigorous immunological response, potentially linked to viral reactivation. The novel association of rs11836509 with lung cancer highlights the imperative for additional investigation into its functional significance. Despite the lack of correlation between EBV IgG and KRAS IgG levels, the interplay between viral reactivation and genetic susceptibility (e.g. SNP rs11836509) may yield a synergistic effect that facilitates disease progression.

These findings underscore the necessity for additional research into the interaction between viral reactivation and genetic determinants in lung cancer. The correlation of SNP rs11836509 with lung cancer indicates its potential as a significant genetic marker for susceptibility, and subsequent research should aim to clarify the functional pathways via which this SNP influences the disease.

Conclusions

While no direct correlation was shown between EBV and KRAS mutations, EBV infection is associated with lung cancer, and rs11836509 may contribute to disease development. Additional research is necessary to clarify these links.

Authors' declaration:

We confirm that all tables and figures in the paper present the findings of the current investigation. The authors have endorsed the ethical considerations for acceptance of Ethical Clearance: Accepted by the Research Ethics Committee and Scientific Committee appointed by the Biology Department, College of Science, University of Baghdad, under reference number Reference No. CSEC/0222/0007) on (29/ 10/ 2023).

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Authors' contributions:

Study conception & design: (Lubna M. Rasoul). Literature search: (Ruqaya K. Abbas). Data acquisition: (Ruqaya K. Abbas). Data analysis & interpretation: (Ruqaya K. Abbas). Manuscript preparation: (Ruqaya K. Abbas). Manuscript editing & review: (Ruqaya K. Abbas and Lubna M. Rasoul).

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دراسة الأجسام المضادة IgG لفيروس إبشتاين بار مع التركيز على تعدد أشكال النوكليوتيدات المفردة كمؤشر حيوي لسرطان الرئة والتهرب المناعي لدى المرضى العراقيين

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الخلاصة:
الخلفية: يُعد سرطان الرئة السبب الرئيسي للوفيات المرتبطة بالسرطان عالميًا، حيث يمثل 18.4% من إجمالي الوفيات. ويترتب على هذا المرض تأثيرات اقتصادية واجتماعية كبيرة على المرضى وعائلاتهم. تم اكتشاف فيروس إبشتاين-بار (EBV) عام 1964، وهو فيروس مُسرطن رئيسي مسؤول عن أكثر من 200,000 حالة سرطان سنويًا و1.8% من الوفيات المرتبطة بالسرطان عالميًا. تم اكتشاف جين KRAS، وهو أحد أعضاء عائلة الجينات المسرطنة RAS، لأول مرة في سرطان الرئة عام 1982 على الكروموسوم 12 (12p11.1–12p12.1).
الأهداف: التحقيق في العلاقات الجزيئية المعقدة بين إيجابية المصل ضد الأجسام المضادة IgG لفيروس إبشتاين-بار ، والمناعة الناتجة عن طفرات جين KRAS، وتعدد أشكال الجينات (rs121913238). يهدف البحث إلى دراسة دور هذه العوامل في مسارات الإشارات المسرطنة، والهروب المناعي، والتغيرات في بيئة الورم الدقيقة، وتأثيرها المشترك على تطور وتقدم سرطان الرئة .
المرضى والطرق: تم جمع عينات من المصل والدم الكامل (n = 100). تم قياس تركيزات الأجسام المضادة IgG ضد فيروس إبشتاين-بار باستخدام تقنية ELISA، تلاها تحليل جزيئي باستخدام تفاعل البوليميراز المتسلسل التقليدي، وتسلسل سانجر لتحديد تعدد أشكال النيوكليوتيدات المفردة في 30 عينة، تم اختيار هذه العينات الثلاثين استنادًا إلى نتائج اختبار ELISA، حيث شملت 15 عينة من المرضى و15 عينة من أفراد أصحاء. استند هذا الاختيار إلى ارتفاع تركيزات الأجسام المضادة IgG لفيروس إبشتاين-بار، وذلك بناءً على فرضية أن المستويات المرتفعة من الأجسام المضادة قد تؤثر على الجين. أما العينات المتبقية، التي استُبعدت من تحليل تعدد الأشكال الجيني، فقد أظهرت تركيزات منخفضة نسبيًا من الأجسام المضادة، مما دفعنا إلى الافتراض بأنها لن يكون لها تأثير كبير.
النتائج: أظهرت مستويات IgG ضد فيروس إبشتاين-بار زيادة كبيرة لدى المرضى مقارنةً بالمجموعة الضابطة (P = 0.0003)، مما يشير إلى احتمال وجود ارتباط بسرطان الرئة. لم يتم الكشف عن تعدد الشكل الجيني المحدد (rs121913238)، ولكن تم تحديد SNP بديل (rs11836509) في 8 عينات (6 مرضى، 2 من المجموعة الضابطة).
الإستنتاج: على الرغم من عدم إثبات وجود ارتباط مباشر بين فيروس إبشتاين-بار وطفرات KRAS، إلا أن عدوى إبشتاين-بار ترتبط بسرطان الرئة، وقد يساهم (rs11836509) SNP في تطور المرض. هناك حاجة إلى مزيد من البحث لتوضيح هذه الروابط.
الكلمات المفتاحية: فيروس إبشتاين-بار؛ KRAS؛ سرطان الرئة؛ الطفرات؛ تعدد الأشكال