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博士の専攻分野の名称	博士（医学）
学位記番号	第 17430 号
学位授与年月日	平成15年1月30日
学位授与の要件	学位規則第4条第2項該当
学位論文名	Epidemiological and pathological studies of Human herpesvirus 8 infection in Thai population （タイ国におけるヒトヘルペスウイルス8の疫学的、病態的研究）
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論文内容の要旨

Objective

Human herpesvirus 8 (HHV-8) or Kaposi's sarcoma associated herpesvirus (KSHV) is a gammaherpesvirus homology to Herpesvirus saimiri and Epstein-Barr virus (EBV). The DNA sequences were first identified in Kaposi's sarcoma (KS) of acquired immunodeficiency syndrome (AIDS) patients and were demonstrated in all clinical forms of KS and other AIDS-associated malignancies e.g. body-cavity based lymphomas or primary effusion lymphoma and multicentric Castleman's diseases. They were also detected in various types of proliferative skin lesions. The detection of HHV-8 infection in Asian countries including Thailand where is an area with high prevalence of HIV infection but rare cases of KS and common cases of skin complication in AIDS patients. Therefore, in this study, HHV-8 infection in Thais was conducted by determining HHV-8 seroprevalence in HIV-1 negative and HIV-1-positive individuals with and without skin diseases.

Methods, Results and Discussion

Immunofluorescence antibody (IFA) assay for detection and titration of anti-lytic and anti-latent HHV-8 antibodies. The lytic and latent HHV-8 antigens (Ag) were prepared from a HHV-8 positive B-cell line, BCBL-1 cells line, Ramos cells were used ad HHV-8 negative antigen control. Anti-lytic antibody (Ab) were detected in 100% of AIDS-KS (n=2), approx. 14% of HIV-1-positive patients (n=434) which was 12% of homosexuals (n=49), 16% of heterosexuals (n=304) and 9% of IDU (n=81) and relatively up to 25% of HIV-1 carriers with skin diseases but low at 8% of HIV-1-negative individuals (n=1018). The geometric mean titers (GMT) were 272 for HIB-1-positive and ranged from 80 to 116 for HIV-1-negative individuals. In contrast to Ab to lytic Ag, anti-latent Ab was detected in only 0.7% of HIV-1-positive (n=434) and only 0.6% of healthy HIV-1-negative subjects (n=515) that were from the north of Ttailand, but in 100% of AIDS-KS (n=2). The GMT for HIV-1-infected patients (320) were similar to those for HIV-1-negative individuals (253). None of samples wes reacted to Ramos cells

Enzyme-linked immunosorbent assay (ELISA) for detection of anti-mixed HHV-8 antibodies. The recomvinant proteins derived from open reading frames (orf) K8.1, orf 59, orf 65 and orf 73 representing immunoreactive lytic-

and latent-cycle proteins of HHV-8 were prepared and mixed as HHV-8 antigens (Ag) for ELISA. 100% of AIDS-KS patients (n=2) and 0.7% of HIV-1 infected patients without KS (n=434) were reactive to these Ag and 0.6% of healthy HIV-1 negative adults (n=515) that were 3 from the north.

IFA assay for detection of anti-K8.1 antibody. The orf K8.1 expressed 293T cell used as antigens were prepared by transient-transfection of plasmid pcDNA 3.1 carrying K8.1 protein encoded gene (pcDNA3.1-K8.1) to the 293T cells. Expression of K8.1 wes checked by IFA using the anti-orf K8.1 Mab. The anti-orf K8.1 antibodies were confirmed in 100% of AIDS-KS patients (n=2) but only in 0.2% of HIV-1 infected subjects without KS (n=434) and 0.2% of healthy HIV-1 engative adults (n=515) that was a sample from the north.

Immunoprecipitation analysis. Immunoprecipitates prepared from HHV-8 seropositive HIV-1 infected patientswith or without skin deseases and from HHV-8 antigens derived from BCBL-1 or B95-8 or Ramos cells were subjected to analyze by SDS-PAGE and autoradiography. HHV-8 specific polypeptides (125, 40 and 34-40 Kda) were recognized by HHV-8 seropositive sera.

Summary

In this study. seroprevalence of HHV-8 infection in the Thai population was determined using different systems. It was found that infection of HHV-8 does occur rarely among both the general and HIV-1 infected populations, based on the concordant reactivity of sera from all assays, which the seroprevalence was less than 1%. However, a marked variation in HHV-8 seroprevalence rate was found depending on assays. Infection rates gradually increased in both the HIV-1-negative and HIV-1 positive population with different antigens used for antibody assays ; from a single orf K8.1 protein to combined-four recombinants proteins to latent forms to lytic forms. In general, the maximum rate was approx. 10% ranged from 8% of the general HIV-1-negative and 14% of HIV-1 infected individuals using a lytic IFA. HHV-8 is likely to be activated in HIV-1 infected patients with skin diseases which the seroprevalence was a little high (25%). The association of HHV-8 in AIDS-KS, even rare cases, was confirmed by all serological and PCR-based assays. Our data suggested that HHV-8 is not coinfected with HIV-1 in HIV-1 carriers. Therefore, it is not an endemic pathogen or might be introduced shortly to Thailand.

論文審査の結果の要旨

ヒトヘルペスウイルス８（HHV-8）は、AIDS 患者のカポジ肉腫病変より同定されたヘルペスウイルスである。現在までのところ、HHV-8 は、カポジ肉腫および AIDS 関連性の悪性疾患の発症およびその病態に関与している可能性が示唆されている。アジア諸国における報告では、HHV-8 の感染率は欧米に比し、非常に低率であるとされている。特に、タイにおいては、HIV 感染率は高率であるのに対し、AIDS 患者におけるカポジ肉腫発症率は非常に低率である。

本論文は、タイにおけるヒトヘルペスウイルス８（HHV-8）の疫学調査を行い、HIV 陽性あるいは、HIV 陰性患者における HHV-8 の感染率を調査したものである。タイには、HHV-8 感染者数は非常に少なく、また HIV 感染者との相関性も認められなかった。欧米における報告では、HIV および HHV-8 の感染ルートは、同じである可能性を示唆しているが、本論文は、タイにおける HHV-8 感染ルートは、HIV 感染ルートとは違っている可能性を見いだしたものである。本論文は、HHV-8 の感染が、HIV 感染の多い、タイにおいては、HIV 感染とは平行していないことを示し、欧米における HHV-8 の感染様式との違いを見いだしたものであり、学位に値するものと考える。