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Human papillomavirus (HPV) DNA is not detected in the peripheral blood cells of patients with cervical carcinoma

Studies on cervical carcinoma have indicated a strong association between specific strains of human papillomaviruses (HPV), most commonly HPV 16 and 18, and cervical cancer.[1] The interplay between the early region proteins E6, and E7 of these two HPV types and the cellular tumour suppressor genes Rb and p53, has been suggested to be relevant for a malignant potential.[2] The classical cytological pap smear is the classical way for early detection of malignant or pre malignant cervical lesions. However, attempts have been made to find other parameters, which will allow early detection of lesions with malignant potential, in order to perform rapid therapeutical measures. Since HPV infection may have a malignant potential, detection of HPV DNA was considered important. DNA hybridisation techniques, including the polymerase chain reaction (PCR) have been used for the detection of HPV DNA in dysplastic and malignant lesions.[3] Recently, the repeated presence of HPV in cervical smears has been suggested to be an important predictive factor for the progression of cervical carcinoma. In addition, in some patients suffering from HPV positive urogenital infections HPV DNA could be detected in the patients' peripheral blood cells (PBL).[4]

The aim of this study was to identify if HPV could be detected in the PBLs of cervical cancer patients, and to determine if this presence could be correlated with the prognosis.

Forty-five patients who had been treated or were presently suffering from a cervical carcinoma were included in this study and their status of disease listed in the table. In parallel these patients were included in a study concerning the correlation of cervical carcinoma and HLA antigens, to be published elsewhere. Genomic DNA was prepared by digesting 8 ml blood (collected in tubes containing EDTA to avoid coagulation) with proteinase K (Boeringer Mannheim) at 42°C overnight and then salted-out with 6M NaCl according to Miller *et al.*[5] This procedure removed the EDTA. For each PCR reaction approximately 500 ng of DNA, corresponding to approximately 10^5 cells was used. A nested general primer two step PCR was performed with the general primer pairs My11/My09 and GP5/GP6 located within the HPV type 16 L1 region as described by Evander *et al.*[3]

No HPV DNA was detected in any of the examined individuals, regardless of their clinical history, as shown in the table. This was not because the DNA material was not sensitive to the PCR reaction as such, since with the PCR technique it was possible to detect the presence of HLA antigens, as also shown in the table. As an HPV positive control for this assay we used an HPV positive laryngeal papilloma (data not shown).

The absence of HPV DNA in PBLs of cervical carcinoma patients was unexpected, since in a recent study HPV DNA was detected in peripheral blood mononuclear cells (PBMCs) in approximately 50% of the patients suffering from urogenital HPV infections.[4] In this previous study, the DNA used for the PCR reaction was purified from 3000 and 7500 PBMCs or purified directly from 20 μl of serum, both from healthy individuals, and from patients with urogenital infections. The patients with urogenital infections were defined as patients with HPV positivity in their cervical smears by PCR in at least two consecutive screenings. One third of these patients were also suffering from condyloma accuminatum of the vulvae. The primers used for PCR amplification corresponded to the E6 open reading frame of HPV. Using the same PCR assay HPV DNA was not detected in any of the individuals in the healthy control group.

In this present study, we have used a slightly different approach. First of all we have examined patients with a history of past or ongoing cervical cancer. Our starting material has been 8 ml of blood. DNA was prepared from the whole sample. Thus, if the virus infected cells were present in a low concentration (1 virus infected cell/10^6-10^7 cells), viral DNA should still have been recovered. Furthermore, although not all the extracted DNA was used in the PCR assay, since papovaviruses given an episomal viral infection, with several copies (50–200) of the virus/infected cell, viral DNA should still have been detected. This has not been the case.

The differences observed between the two studies could be due to the fact that the patient groups examined were derived from different populations, or different patient groups. Whether or not the use of different primers for the PCR reaction plays a role may be debated.

Absence of HPV DNA in PBLs of patients with cervical cancer

Disease status:	*No. of patients*	*HPV positive*	*HLA DQ positive*
Progressive squamous cell carcinoma	22	0/22	22/22
Progressive adenocarcinoma	5	0/5	5/5
Non progressive squamous cell carcinoma	9	0/9	9/9
Non progressive adenocarcinoma	7	0/7	7/7
"Healthy patients"*	8	0/8	8/8
Total no.	45	0/45	45/45

*Patients with a normal PAD

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I LEWENSOHN-FUCHS
Z BERKE
D WESTER
T DALIANIS
Dept. of Immunology, Microbiology, Pathology, and Infectious Diseases
K ELFGREN
Dept. of Gynaecology and Obstetrics, Karolinska Institutet, Huddinge Hospital F79, 141 86 Huddinge, Sweden

Correspondence to: Dr T Dalianis.

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Ciprofloxacin resistant gonococci arriving from Thailand

In an attempt to overcome the increasing isolation of penicillin resistant gonococci (both chromosomal and plasmid-mediated), some genitourinary medicine clinics in London now use single-dose oral ciprofloxacin as first-line therapy. This is in line with the World Health Organisation's 1989 recommendations.[1] Ciprofloxacin has the advantage of costing less than spectinomycin or third-generation cephalosporins. Unfortunately, there have been recent reports of resistance to ciprofloxacin with associated clinical treatment failures in London.[2]

We report a 36 year old lorry driver who presented with uncomplicated gonococcal urethritis having just returned from a two week holiday in Thailand where he admitted to having unprotected sexual intercourse with a Thai female. He had not received antibiotics in the previous three months. Staining of his purulent urethral discharge demonstrated Gram negative intracellular diplococci. He was treated empirically with spectinomycin 2 g i.m. and was cured both clinically and microbiologically.

Neisseria gonorrhoeae isolated from the pus at 48 hours exhibited low-level resistance to penicillin (MIC 0·5 mg/l, β-lactamase negative), resistance to tetracycline (MIC 4 mg/l) and decreased susceptibility to ciprofloxacin (MIC 0·25 mg/l). The isolate was fully sensitive to cefotaxime (0·015 mg/l) and spectinomycin (32 mg/l). A growth requirement for proline and expression of the protein 1B-2 serovar were demonstrated by conventional typing.

There is an increasing trend to use oral rather than parenteral treatment for uncomplicated gonococcal infection, hence the current popularity of ciprofloxacin. Taking an accurate travel history from patients with gonorrhoea is crucial in deciding which is the most appropriate first-line agent to prescribe in order to minimise the risk of treatment failure. Gonococci with markedly reduced susceptibility to ciprofloxacin (MIC $\geqslant$2 mg/l) have been reported in studies from South-East Asia. One study from the Phillipines reported an MIC_{90} for ciprofloxacin of 0·25 mg/l[3] and another in Thailand reported 0·3% of gonococcal isolates to have a ciprofloxacin MIC $\geqslant$2 mg/l.[4] Gonorrhoea treatment failures have been associated with ciprofloxacin MICs exceeding 0·12 mg/l.[2] In Thailand, a recent study showed 9% of gonococci to be spectinomycin resistant (MIC $\geqslant$128 mg/l) whereas 100% of isolates were susceptible to cefotaxime.[4] Worldwide, resistance to broad-spectrum cephalosporins is rare. Despite the success with spectinomycin in our patient, it would be more logical for patients acquiring gonorrhoea in South-East Asia to be treated empirically with single-dose therapy using a third generation cephalosporin such as ceftriaxone (i.m.), cefotaxime (i.m.) or cefixime (oral). Spectinomycin and ciprofloxacin may be more appropriate as second-line agents. There is a need for continued antibiotic susceptibility surveillance of *N gonorrhoeae* isolates originating from the tropics in order to prevent dissemination of multi-resistant gonococci into the United Kingdom.

DA LEWIS
GE FORSTER
BT GOH
Ambrose King Centre, Royal London Hospital, Whitechapel, London E1 1BB, UK

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Suitability of *Neisseria gonorrhoeae* lipooligosaccharides for epidemiological studies

Although the lipooligosaccharides (LOSs) of *N gonorrhoeae* are multicomponent and display considerable interstrain heterogeneity,[1] the components of the LOSs of individual *N gonorrhoeae* strains have been shown to