Chlamydia trachomatis infection in women with lichen sclerosus vulvae and vulvar cancer

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Abstract

OBJECTIVE: Chronic infections in the urogenital area often precede or coexist with vulvar cancer. A strong connection between some tumours and the-appearance of Chlamydia trachomatis infection has been observed, but there is little information concerning a connection of that infection with vulvar cancer and lichen sclerosus vulvae (LS).

The aim of this study was the analysis of frequency of antigens appearance and antibodies of IgM and IgG Chlamydia trachomatis in patients with vulvar cancer and LS and we wanted to find the correlation between Chlamydia trachomatis infection and vulvar cancer and LS.

METHODS: 80 women treated in the Clinic of Vulva Diseases at the Department and Clinical Ward of Gynaecology, Obstetrics and Oncological Gynaecology in Bytom, in the Silesian Medical University in Katowice were divided into two groups – 30 were treated for vulvar cancer and 50 were treated because of LS. We took bacterial smears vagina and cervical smears for presence of Chlamydia trachomatis antigens and peripheral blood to mark antibodies of IgM and IgG Chlamydia trachomatis.

RESULTS: Chlamydia trachomatis antigen was found in 20% women with vulvar cancer and in 12% women with LS (p>0.05). In 13.3% cases with vulvar cancer we observed IgM Chlamydia trachomatis antibodies. In the group with LS IgM antibodies appeared in 16% women (p>0.05). In 50% patients with vulvar cancer in blood serum we observed IgG Chlamydia trachomatis antibodies, and in 16% women with LS (p<0.001).

CONCLUSIONS: Previous Chlamydia trachomatis infection can lead to vulvar carcinogenesis.
INTRODUCTION

Vulvar cancer accounts for 3–5% of all malignant tumours of women reproductive organs, and in almost 90–95% of cases it is carcinoma planoepitheliale with hornification or without hornification (Gastrell et al. 2001; De Koning et al. 2008; Ciszko et al. 2006). The highest incidence for this tumour worldwide is at the age between 70 and 80, but in Poland vulvar cancer is most often found in women between 60 and 70 (Bierkiewicz et al. 2002). Rarely, vulvar cancer is found in women below 30 years and it develops probably because of endothelial neoplasia caused by human papillomavirus infection (HPV) (Carter et al. 1993; Al-Ghamdi et al. 2002; Basta et al. 1999; Joura et al. 2001). In elderly women cancer develops mostly following chronic, neglected inflammation of vulvae (De Koning et al. 2008).

Many authors draw attention to a connection between appearance of vulvar cancer and lichen sclerosus vulvae (LS) (Carli et al. 2008; Smith et al. 2004). In about 4% of cases vulvar cancer can develop from LS, which is a chronic disease of unknown etiology proceeding with fibrosis, inflammation and reduction of cells (Cocayne et al. 1998).

More and more frequently attention is drawn to the role of chronic infection in the urogenital area in the development of different vulvar diseases including tumours of external sexual organs of women. Infections often precede or coexist with vulvar cancer and because of the influence on organism resistance they facilitate colonization of subsequent pathogens (Olejek 2002; Canavan et al. 2002).

Chlamydia trachomatis infection is now thought to be one of the most common reason for sexually transmitted diseases. In Europe, the prevalence of chlamydial infection among young females ranges between 4.1% and 25% (Kucinskiene et al. 2006). On the basis of antigen differences we distinguish a dozen serological types. According to the type of Chlamydia trachomatis it can be a reason of endemic conjunctivitis, lymphogranuloma venereum or infections of urinary tract and sexual tract (Zdrodowska-Stefonow et al. 2003). A strong connection between some tumours and the appearance of Chlamydia trachomatis infection has been observed (Anttila et al. 2001; Wallin et al. 2002).

But there is scant information concerning a connection between this infection and vulvar cancer and lichen sclerosus vulvae.

The aim of this study was the analysis of frequency of antigens appearance and antibodies of IgM and IgG Chlamydia trachomatis in patients with vulvar cancer and lichen sclerosus vulvae and we wanted to find the correlation between Chlamydia trachomatis infection and vulvar cancer and lichen sclerosus vulvae.

MATERIAL AND METHODS

We examined a group of 80 women treated in the Clinic of Vulva Diseases at the Department and Clinical Ward of Gynaecology, Obstetrics and Oncological Gynaecology in Bytom, in the Silesian Medical University in Katowice.

Women were divided into two groups. In the first group 30 were treated for vulvar cancer and in the second 50 were treated because of lichen sclerosus vulvae (LS).

From all patients we took additionally 5 ml of peripheral blood for clot to mark antibodies of IgM and IgG Chlamydia trachomatis. Antibodies were determined with ELISA method using VIR – ELISA Test Anti Chlamydia IgG and IgM (Viro-Immun Labor-Diagnostika Gmbh) set.

This study was approved by the institutional review boards of the Silesian Medical University in Katowice – Bioethical Board (nr 013-212/01).

Written informed consent was obtained from all patients.

A statistic analysis was carried out using Statistica 6.0 data analysis system. Statistical significance was defined as a p-value <0.05.

RESULTS

The average age of patients with vulvar cancer was 65.5 years and average age of patients with lichen sclerosus vulvae was 59.8 years. Age difference between these two groups was statistically significant (p<0.01).

Chlamydia trachomatis antigen was found in 6 women (20%) with vulvar cancer and in 6 women (12%) with LS. There were no statistically significant differences in appearance of Chlamydia trachomatis antigen between these two groups. (Table 1).

In 4 patients (13.3%) with vulvar cancer we observed IgM Chlamydia trachomatis antibodies. In the group with lichen sclerosus vulvae IgM antibodies appeared in 8 women (16%). There were no statistically significant differences in appearance of Chlamydia trachomatis IgM antibodies between these two groups. (Table 2).

In 15 patients with vulvar cancer (50%) in blood serum we observed IgG Chlamydia trachomatis anti-

#### Table 1. Chlamydia trachomatis antigens in women with vulvar cancer and LS.

<table>
<thead>
<tr>
<th></th>
<th>AG (-)</th>
<th></th>
<th>AG (+)</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>17</td>
<td>74%</td>
<td>6</td>
<td>26%</td>
<td>0.232</td>
</tr>
<tr>
<td>LS</td>
<td>37</td>
<td>86%</td>
<td>6</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

AG - antigens, (-) absent, (+) present, Ca - cancer, LS – lichen sclerosus vulvae.
bodies, and in 8 women with LS (16%). The difference between these two groups was statistically significant ($p<0.001$). (Table 3).

In bacterial smears from women with vulvar cancer we observed most often *Escherichia coli* (26.6%), *Proteus mirabilis* (26.6%), *Streptococcus β haemoliticus* group B (26.6%) and *Pseudomonas aeruginosa* (13.3%). In women with LS most often there appeared *Escherichia coli* (38%), *Proteus mirabilis* (32%), *Streptococcus β haemoliticus* group B (24%) and *Staphylococcus haemoliticus* (12%). There were no statistically significant differences in appearance of individual pathogens between the two groups ($p>0.05$).

## DISCUSSION

Chronic inflammation can be a factor initiating carcinogenesis (Olejek 2002; Kucinskiene et al. 2006; Boyle et al. 2003; Gastrell et al. 2001). Conditions within the urogenital area create the optimal environment for development of bacteria, mycotic fungi and also viral infections (Velemínský et al. 2008). Long lasting inflammatory processes disturb vulvar trophic, causing pruritis often leading to mechanical damage of epithelium (Pisani et al. 1990). Increased moistness and high temperature in the urogenital area facilitate bacteria colonization (Velemínský et al. 2008).

Vulvar cancer is often observed in women from lower social classes, unkempt with low hygienic standards (De Koning et al. 2008).

Chronic HSV2, HPV and *Chlamydia trachomatis* infections, which often precede or coexist with vulvar cancer, significantly influence development of pathological bacterial flora and decrease immunologic resistance (Ciszko et al. 2005; Gastrell et al. 2001). Human Papilloma virus is diagnosed more often in VIN than in invasive vulvar cancer. However, in the case of HPV type 16/18 the presence of E6 and E7 encoding so-called oncoproteins, which inactivate protein products of cells of antioncogenes, suggesting that they participate in the process of carcinogenesis (De Koning et al. 2008).

*Chlamydia trachomatis* is a unique obligate intracellular bacterium that remains the leading cause of sexually transmitted bacterial diseases and preventable blindness worldwide. The course is often poorly in symptoms or symptomatic – free (Mardah et al. 2001). Defensive reactions which start as a result of *Chlamydia trachomatis* infection are still not fully recognized. Chlamydial 60-kDa heat shock proteins (cHSP60s) are known to play a prominent role in the immunopathogenesis of disease. Heat shock protein 60 (HSP60) plays an important role in the protein folding of prokaryotic and eukaryotic cells. Most papers published on chlamydial cHSP60 concern its role in immune response during infection. In the last decade, exposure to *Chlamydia trachomatis* has been consistently associated with the development of cervical and ovarian cancer. Moreover, it has been suggested that chlamydial cHSP60 may have an anti-apoptotic effect during persistent infection (Di Felice et al. 2005; Pavonen et al. 2003).

Many authors believe that chronic inflammation caused by *Chlamydia trachomatis* can be responsible for development of pre-cancerous conditions (Anttila et al. 2001). Attention is paid to the fact that antibodies level directed against *Chlamydia trachomatis* correlate with intensity of pathological changes in tissues (Smith et al. 2002; Koskela et al. 2000). Infections of both *Chlamydia trachomatis* and HPV correlate with high expression of Ki 67 in epithelium. *Chlamydia trachomatis* infection also increased the expression of HPV16 in CIN I. These results suggest that *Chlamydia trachomatis* infection modifies the activity of viruses (Fisher, 2002).

A correlation of *Chlamydia trachomatis* infection with cervical cancer is often described (Anttila et al. 2001; Wallin et al. 2002; Smith et al. 2002; Koskela et al. 2000). Schlott et al. (2005) observed that tissues respond to *Chlamydia trachomatis* with a strong down-regulation of caveolin-1 mRNA and a light up-regulation of C-myc mRNA. These changes were independent of the HPV high-risk types. Their study reveals possible mechanisms by which *Chlamydia trachomatis* infection may contribute to neoplastic changes in the transformation of uterine cervix. Some authors suggest that past or chronic persistent infection with chlamydia may be a risk factor for ovarian cancer (Ness et al. 2003).

Information concerning co-appearance of *Chlamydia trachomatis* with vulvar cancer or lichen sclerosus vulvae is extremely poor. Epidemiologic studies suggest that *Chlamydia trachomatis* infection also confers increased risk for cervical squamous cell carcinoma (SCC) in serotype-specific (Anttila et al. 2001; Madeleine et al. 2007). Madeleine et al. (2007) observed that there is an association between specific serotypes of *Chlamydia trachomatis* and SCC for 6 of the 10 serotypes.

### Tab. 2. Chlamydia trachomatis antibodies IgM in women with vulvar cancer and LS.

<table>
<thead>
<tr>
<th></th>
<th>IgM (−)</th>
<th>IgM (+)</th>
<th>$p$-value</th>
</tr>
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<tbody>
<tr>
<td>Ca</td>
<td>25</td>
<td>86%</td>
<td>4</td>
</tr>
<tr>
<td>LS</td>
<td>45</td>
<td>85%</td>
<td>8</td>
</tr>
</tbody>
</table>

AG - antigens, (−) absent, (+) present, Ca - cancer, LS – lichen sclerosus

### Tab. 3. Chlamydia trachomatis antibodies IgG in women with vulvar cancer and LS.

<table>
<thead>
<tr>
<th></th>
<th>IgG (−)</th>
<th>IgG (+)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>25</td>
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In our research a more frequent appearance of antibodies IgG class against Chlamydia trachomatis was observed in the group of patients with vulvar cancer than in women with lichen sclerosus vulvae and the difference between the observed groups was statistically significant (p<0.05). Chronic disease seems to coexist with appearance of vulvar cancer. It is often stressed that abnormal bacterial flora is a source of compounds potentially carcinogenic. It has been observed that Chlamydia trachomatis infection stimulates development of glandular epithelium in cervix and increased secretion of mucous, leading to exchange of stratified squamous epithelium into glandular epithelium and to changes of pre –cancerous character (Anttila T, 2001; Wallin et al. 2002; Koskela et al. 2000).

CONCLUSION

Previous Chlamydia trachomatis infection can lead to vulvar carcinogenesis.

ACKNOWLEDGEMENT

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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