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

Anita Olejek [1], Iwona Kozak-Darmas [1], Sylwia Kellas-Sleczka [1,2], Anna Jarek [1], Andrzej Wiczkowski [3], Wojciech Krol [4], Krystyna Stencel-Gabriel [5]

1 Department and Clinical Ward of Gynecology, Obstetrics and Oncological Gynecology in Bytom, in the Silesian Medical University in Katowice,
2 Department of Brachytherapy, Maria–Skłodowska Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch
3 Department of Microbiology and Immunology in Zabrze, in the Silesian Medical University in Katowice,
4 Department of Medical Biology in Zabrze, in the Silesian Medical University in Katowice,
5 Department of Pediatrics, Bytom, Medical University of Silesia.

Correspondence to: Anita Olejek, MD.
The Department and Clinical Ward of Gynaecology,
Obstetrics and Oncological Gynaecology SUM,
ul. Batorego 15, 41-902 Bytom, Poland.
PHONE: +48 032 7861540; FAX: +48 032 7861;
E-MAIL: bytomobstgyn@sum.edu.pl, klingin1@interia.poczta.pl

Submitted: 2009-01-20 Accepted: 2009-05-15 Published online: 2009-11-12

Key words: ***chlamydia trachomatis*; lichen sclerosus vulvae**

Neuroendocrinol Lett 2009; **30**(5):671–674 **PMID:** 20035265 NEL300509A20

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 trachomastis*.

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.

ORIGINAL ARTICLE

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 (Bieńkiewicz *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 proceeeding 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 theappearance of *Chlamydia trachomatis* infection has been observed (Anttila *et al.* 2001; Wallin *et al.* 2002).

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

	AG (–)		AG (+)		*p*-value
	n	%	n	%	
Ca	17	74%	6	26%	0.232
LS	37	86%	6	14%	

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

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 bacterial smears from lateral walls of vagina and cervical smears for presence of *Chlamydia trachomatis* antigens on liquid Transport base "Chlamydia Specimen Collection Kit" (DAKO). From all women we took additionally 5 ml of peripheral blood for clot to mark antibodies of IgM and IgG *Chlamydia trachomastis*. 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-

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).

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

	IgM (–)		IgM (+)		*p*-value
	n	%	n	%	
Ca	25	86%	4	14%	0.867
LS	45	85%	8	15%	

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

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

	IgG (–)		IgG (+)		*p*-value
	n	%	n	%	
Ca	25	86%	4	14%	0.867
LS	45	85%	8	15%	

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

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.* 2006; 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 belive 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 expession 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 sero-

types: B, D, E, G, I and J but not for C, F, H, and K . Zereu *et al.* (2007) did not find a correlation between adenocarcinoma of the uterine cervix and *Chlamydia trachomatis* infection.

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

Supported by a grant KBN NN-6-277/06

Conflict of interest statement

The authors declare that there are no conflicts of interest.

REFERENCES

1 Al-Ghamdi A, Freedman D, Miller D Poh C, Rosin M, Zhang L *et al.* (2002). Vulvar quamosus cell carcinoma in young women: a clinicopathology study of 21 cases. Gynecol Oncol. **84**: 94–101.

2 Anttila T, Saikku P, Koskela P, Bloigu A, Dillner J, Ikäheimo I *et al.* (2001). Serotypes of Chlamydia trachomatis and risk for development of cervical squamosus cell carcinoma. Jama. **285**: 47–51.

3 Basta A, Adamek K, Pawlak M, Przeszlakowski D (1999). Incidence of precancerous states in carcinomas of the vulva in young woman. Przegl Lek. **56**: 20–22.

4 Bieńkiewicz A, Gottwald L, Akoel KM, Lech W, Welfel J, Suzin J (2002). Clinical analysis of 105 cases of vulvar cancer. Ginekol Pol. **76**(11): 913–918.

5 Boyle P, Leon ME, Maisonneuve P, Autier P (2003). Cancer control in women. Update 2003. Int J Gynaecol Obstet. **83**: 179–202.

6 Canavan TP, Cohen D (2002). Vulvar cancer. Am Fam Physician. **66** (7): 1269–74.

7 Carli P, De Magnis A, Mannoe F, Botti E, Taddei G, Cattaneo A (2003). Vulvar carcinoma associated with lichen sclerosus. Experience at the Florence, Italy. Vulvar Clinic. J Reprod Med. **48**(5): 313–318.

8 Carter J, Carlson J, Fowler J, Hartenbach E, Adcock L, Carson L*et al*. (1995). Invasive vulvar tumors in young women. A disease of immunosuppressed? Gynecol Oncol. **51**: 307–10.

9 Ciszko B, Pochwalowski M, St Gabryś M (2006). Risk factors and clinical characteristic patients with vulvar cancer. Ginekol Pol. **77**(12): 914–921.

10 Cocayne SE, Shah M, Slater DN, Harrington CI (1998). Spindle and pseudoglandular squamosus cell carcinoma arising in lichen sclerosus of the vulva. Br Dermatol. **138**: 695–697.

11 Di Felice V, David S, Cappello F, Farina F, Zimmo G (2005). Is chlamydial heat shock protein 60 a risk factor for oncogenesis? Cell Mol Life Sci. **62**(1): 4–9.

12 Fisher N (2002). Chlamydia trachomatis infection in cervical intraepithelial neoplasia and invasive carcinoma. Eur J Gynaecol Oncol. **23**(3): 247–250.

13 Gastrell FH, McConell DT (2001). Human papillomavirus and intra-epithelial neoplasia. Best Pract Res Clin Obst Gynaec. **15**: 769–782.

14 Joura EA, Losch A, Haider-Angeler MG, Breitenecker G, Leodolter S (2001). Trends in vulvar neoplasia. Increasing incidence of vulvar intraepithelial neoplasia and squamosus cell carcinoma of the vulva in young women. J Reprod Med. **45**(8): 613–615.

15 De Koning MN, Quint WG, Pirog EC (2008). Prevaelnce of mucosal and cutaneus human papillomaviruses in different histologic subtypes of vulvar cancer. Mod Pathol. **21**(3): 334–344.

16 Koskela P, Anttila T, Bjorge T, Brunsvig A, Dillner J, Hakama M *et al*. (2000). Chlamydia trachomatis infections as a rosk factor for invasive cervical cancer. Int J Cancer. **85**: 35–39.

17 Kucinskiene V, Sutaite I, Valiukeviciene S, Milasauskiene Z, Domeika M. (2006). Prevalence and risk factors of genital Chlamydia trachomatis infection. Medicina (Kaunas). **42:** (11): 885–894.

18 Madeleine MM, Anttila T, Schwartz SM, Saikku P, Leinonen M, Carter JJ *et al*. (2007). Risk of cervical cancer associated with Chlamydia trachomatis antibodies by histology, HPV type and HPV cofactors. Int J Cancer. **120**(3): 650–655.

19 Mardah PA, Novikova N (2001). Chlamydia trachomatis infections – a major concern for reproductive health. Where do we stand regarding epidemiology, pathogenesis and therapy? Eur J Contracept Reprod Health Care. **6**: 115–126.

20 Ness RB, Goodman MT, Shen C, Brunham RC (2003). Serologic evidence of past infection with Chlamydia trachomatis, in relation to ovarian cancer. J Infect Dis. **187**(7): 1147–1152.

21 Olejek A (2002). Bacterial flora in vulvar carcinoma with HPV 16 or HPV 18 infection. Hung J Gynaecol Oncol. **2:** 173.

22 Pavonen J, Karunakaran KP, Noguchi Y, Anttila T, Bloigu A, Dillner J *et al*. (2003). Serum antibody response to the heat shock protein 60 of Chlamydia trachomatis in women developing cervical cancer. Am J Obstet Gynecol. **189**(5): 1287–1292.

23 Pisani P, Parkin DM, Munoz N, Ferlay J (1997). Cancer and infections: estimates of the attributable fraction in 1990. Cancer Epidemiol Biomarkers Rev. **6**: 387–400.

24 Schlott T, Eiffert H, Bohne W, Landgrebe J, Brunner E, Spielbauer B *et al*. (2005). Chlamydia trachomatis modulates expression of tumor suppressor gene caveolin-1 and oncogene C-myc in the transformation zone of non-neoplastic cervical tissue. Gynecol Oncol. **98**(3): 409–419.

25 Smith YR, Haefner HK (2004). Vulvar lichen sclerosus: pathophysiology and treatment. Am J Clin Dermatol. **5:** 105–125.

26 Smith JS, Herrero R, Bosetti C, Muñoz N, Bosch FX, Eluf-Neto J *et al*. (2002). Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. J Natl Cancer Inst. **94**: 1592–1593.

27 Velemínský M Jr, Přádná J, Velemínský M Sr, Tošner J (2008). Relationship of amniotic-type placentainflammation to pPROM, PROM and risk of early onset neonatal sepsis Neuroendocrinol Lett . **29** (4): 447–450.

28 Velemínský M Jr, Stránský P, Velemínský M Sr, Tošner J (2008). Relationship of IL-6, IL-8, TNF and sICAM-1 levels to PROM, pPROM, and the risk of early-onset neonatal sepsis. Neuroendocrinol Lett. **29**(3): 303–311.

29 Wallin KL, Hallmans G, Luostarien T, Angström T, Anttila T, Bergman F *et al*. (2002). A population-based prospective study of Chlamydia trachomatis infection and cervical carcinoma. Int J Cancer**. 101**: 371–374

30 Zereu M, Zettler CG, Cambruzzi E, Zelmanowicz A (2007). Herpes simplex virus type 2 and Chlamydia trachomatis in adenocarcinoma of the uterine cervix. Gynecol Oncol. **105**(1): 172–175.

31 Zdrodowska-Stefonow B, Ostaszewska-Puchalska I, Pucio K (2003). The immunology of Chlamydia trachomatis. Arch Immunol Ther Exp. **51:** 289–294.