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ORIGINAL ARTICLE

Interleukin IL-1α, IL-6, IL-8, IL-10 Expression in Different Staging of Cervical Intraepithelial Neoplasia

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Summary
Introduction. Cervical cancer is the fourth most common form of cancer in women [19]. The precancerous stages are divided into three distinctive stages, labelled cervical intraepithelial neoplasia (CIN) I, II and III. One of the aetiological factors is chronic inflammation in cervical tissue, most often induced by Human papilloma virus (HPV). 88,5% of the patients regress from low grade intraepithelial changes to unchanged epithelium [14]. It has been proposed that cytokine balance plays a key role in the development of high grade epithelial changes (CIN I – CIN III) in the remaining 11.5% of patients, however, the exact trigger of this event remains to be found.
Aim of the Study. The aim of the study was to determine three pro-inflammatory (IL-1α, IL-6, IL-8) and one anti-inflammatory (IL-10) interleukin expression in different CIN *cervix uteri* biopsies.
Material and methods. 16 biopsies were obtained with different CIN staging: one with CIN I stage, five with CIN II stage and 10 with CIN III stage. The samples were stained with haematoxylin and eosin and immunohistochemistry for IL-1α, IL-6, IL-8 and IL-10. Slides were evaluated semi-quantitatively grading the intensity of positively stained structures in the visual field.
Results. Examination of the samples yielded the following: IL-1α expression increased from CIN II to CIN III in squamous epithelium, while IL-8 expression decreased. A few IL-1α containing inflammatory cells were found in all CIN stages. IL-8 expression in subepithelium and the number of inflammatory cells decreased from CIN II stage to CIN III, although, it increased in the blood vessel endothelium.
Conclusions. There was constant moderate expression of both IL-6 and IL-10 during all CIN stages, except for inflammatory cells, where IL-6 expression was high during all stages, yet there were few IL-10 containing cells during CIN. The balanced expression of both cytokines suggests that pro- and anti-inflammatory cytokine balance has an important role in CIN morfopathogenesis. The high expression of IL-6 in inflammatory cells and constant expression trough CIN staging indicates sustentation of chronic inflammation and production of other cytokines, such as IL-8, IL-1α. The variable IL-8 expression and its decrease in CIN III stage suggests the depletion of IL-8 production. The high expression of cytokines in blood vessel endothelium indicates their important role in CIN morfopathogenesis.
Key words: cervix, CIN, interleukins, cytokines.

INTRODUCTION

The cervical cancer is the fourth most common cancer in women (19). Even with national screening methods, in 2015 according to The Centre for Disease Prevention and Control of Latvia there were 22.8 deaths from cervical cancer per 100 000 women (43).

One of the main causes for premalignant epithelial lesions is chronic inflammation. For cervical intraepithelial lesions, the most common cause is an infection with the Human papilloma virus (HPV), especially high-risk strains 16 and 18 (10,13). Approximately 9 out of 10 patients have a co-existing HPV infection (22). The virus exhibits a tropism for cervical squamous cells (26). The pathogenesis of HPV induced cervical lesions includes imbalance of cytokine expression in epithelium, fibroblasts, endothelium and lymphocytes.

88.5% of the patients regress from low grade epithelial changes to unchanged epithelium (14). It has been proposed that cytokine balance plays a key role in the development of high grade epithelial changes (CIN II – CIN III) in the remaining 11.5% of patients, however, the exact trigger of this event remains to be found.

Research into the field of the immunological aspects of CIN pathogenesis is scarce, especially in the field of pro- and anti-inflammatory cytokine spectrum and correlation in cervical tissues during, and through the progression of the stages of CIN.

IL-1α is a pro-inflammatory cytokine with dual – anti-tumour and tumour invasiveness promoting characteristics (29,32,37). In normal physiological conditions, IL-1α is produced by mononuclear phagocytes, endothelial cells, keratinocytes and neutrophils. IL-1 indirectly activates T lymphocytes by enhancing IL-2 production. It also stimulates leukocyte adherence to the endothelium by upregulation of ICAM-1, VCAM-1 and E-selectin (16). According to different research data, the expression of IL-1α is higher in CIN compared to healthy *cervix uteri* tissue (7,23,30), and it is even higher in CIN III compared to CIN I (18,30). It has an ability to induce normal and tumour cell growth (4,7,12,37). In CIN with a co-existent HPV infection an increased number of cells expressing IL-1α are seen, because HPV-16, -18 stimulates IL-1α release in keratinocytes, and IL-1α stimulates proliferation of immortal and malignant

cervical epithelial cells (4,23,49). However, reduced IL-1α expression in infected cell lines compared to non-infected cell lines may also be observed (29,50). There is an increase in IL-6 secretion in carcinoma cells (11), as well the enhanced release of IL-8 in immortal cells due to the presence of IL-1α (4,50).

IL-6 is a pro-inflammatory immune response mediator, which induces and stimulates humoral immunity (15). In normal physiological conditions, IL-6 is expressed by mononuclear phagocytic cells, T and B lymphocytes, fibroblasts, endothelial cells and keratinocytes (16).

IL-6 is a potent cancerogenesis mediator, as it inhibits apoptosis and increases VEGF production via SAT3 pathway consequently increasing angiogenesis thus promoting tumour growth (46,48). IL-6 induces expression of IL-1α (12) and additionally mediates the expression of IL-8 (34). This explains why there is a correlation between the expression of IL-6 and IL-8 – both are more expressed in diseased tissues. Different studies agree that IL-6 expression in cervical tissues is higher during CIN compared to healthy specimens (3,6,34,42,45).

IL-8 is a pro-inflammatory cytokine, mostly secreted by immune cells as macrophages, monocytes, T cells and NK cells. It is stored in the blood vessel endothelium (34). Interestingly, within normal tissue IL-8 is more commonly found in macrophages, but in CIN it is more prominent in lymphocytes (11). Evidence is inconclusive whether the highest expression of IL-8 is found in CIN II-CIN III (7,30) or in CIN I (11). It must be noted that the expression of IL-8 is higher in CIN when compared to normal tissues (7,11,24,30,42).

IL-8 secretion and hypoxia of the tissue is a linked process – oxygen deprivation increases IL-8 production (27). Therefore, high expression of IL-8 in the tumour stroma suggests hypoxia, an active vascularization process and a possible metastatic involvement. IL-8 might also be a downregulating factor in cell apoptosis (27,28).

IL-10 is an anti-inflammatory cytokine, normally detected in monocytes, macrophages, B lymphocytes, Th2 lymphocytes, eosinophils, mast cells and keratinocytes (34). It is stated that IL-10 expression increases from CIN I to CIN III and cancer (5,8,9,35,42,45). Increased IL-10 expression in cells indicates impaired HPV clearance, as it has an immunosuppressive action (2,8,9,20,34). IL-10 decreases secretion of pro-inflammatory cytokines IL-6 and IFN gamma (34). However, there are many sources that state that the expression of IL-10 is highest in CIN I, which decreases during CIN II and CIN III (3,31,40). This could be explained by the initial response to the infection by raising cytokine levels in tissue, causing a rise in cytokine levels, leading further on to high grade lesions. Yet, the anti-inflammatory characteristics of IL-10 (34) make it more plausible that IL-6 in CIN I acts as an oncogenesis potentiating factor and later on the expression of cytokines is disrupted altogether (3,15,31).

AIM OF THE STUDY

The aim of the study was to determine three pro-inflammatory (IL-1α, IL-6, IL-8) and one anti-inflammatory (IL-10) interleukin expression in different CIN *cervix uteri* biopsies.

MATERIAL AND METHODS

The study included 16 *cervix uteri* biopsy materials from patients aged 28 to 58 years, of those: one biopsy sample was CIN I, five were CIN II stage and ten were CIN III stage.

The study was approved by the Ethical Committee at Riga Stradins University (permit issued on 20.10.2011.). Cervical biopsies were fixed in Stefanini's solution, dehydrated and embed in paraffin. Three-micrometre-thick sections were prepared from each tissue specimen and stained routinely with haematoxylin and eosin and with immunohistochemistry method (IMH), which was performed for interleukin 1alpha (IL-1α) (orb308737, 1:100; Biorbyt, UK), interleukin 6 (IL-6) (SC-130326, 1:50; Santa Cruz Biotechnology, USA), interleukin 8 (IL-8) (orb39299; 1:100, Biorbyt, UK) and interleukin 10 (IL-10) (250713; 1:100, Abbiotec, USA).

Interleukin expression in squamous epithelium, stroma under the epithelium, cylindrical epithelium, stroma under cylindrical epithelium, blood vessel endothelium and inflammatory cells was assessed.

The results were evaluated semiquantitatively by grading the appearance of positively stained cells in the visual field (36). Few positive cells were labelled with +, moderate number of positive cells in the visual field were labelled with ++, numerous positive cells in the visual field were labelled with +++ and abundance of positive structures in the visual field were marked with ++++.

For visual illustration, Leica DC 300F digital camera and image processing, and analysis software Image Pro Plus (Media Cybernetics, Inc., Rockville, MD, USA) was used.

RESULTS

Routine evaluation of the slides revealed inflammatory cell infiltration, consisting of both mononuclear cells and lymphocytes which were found in both the epithelium and the underlying stroma. Some slides revealed cystic changes of cervical glands.

Number of IL-1α containing cells in squamous and cylindrical epithelium increased from a few (+) in CIN II stage to moderate number of cells (++) in CIN III stage (Table 1, Figure 1). During all CIN stages there were a few (+) IL-1α containing inflammatory cells (Figure 2).

IL-6 was moderately (++) expressed in all three CIN stages in cylindrical and squamous epithelium, also found in the underlying stroma and blood vessel endothelium (Figure 3). There were numerous IL-6 expressing inflammatory cells trough all CIN staging (Table 2, Figure 4).

In CIN II stage the number of IL-8 positive epitheliocytes was moderate (++), and it decreased in CIN III stage to a few (+) IL-8 positive epitheliocytes in squamous and

cylindrical epithelium. The expression of IL-8 in CIN I and CIN II was moderate in subepithelium, blood vessel endothelium and inflammatory cells, decreasing in CIN III stage to a few (+), except the inflammatory cells, where the expression increased (Table 3, Figure 5).

Finally, IL-10 positive cells were mostly a moderate number (++) in all cases, except in blood vessel endothelium, where it increased from moderate (++) in CIN II to numerous (+++) in CIN III (Figure 6). However, a few (+) IL-10 positive inflammatory cells were found trough all CIN stages (Table 4, Figure 7).

Table 1. IL-1α expression in different CIN stages

	Squamous epithelium	Subepithelium	Cylindrical epithelium	Subepithelium	Blood vessel endothelium	Inflammatory cells
CIN I	+++	+	-	-	++	++
CIN II	+	+	+	+	+	+
CIN III	++	+	++	++	++	+

Abbreviations in the Table: CIN – cervical intraepithelial neoplasia.

Table 2. IL-6 expression in different CIN stages

	Squamous epithelium	Subepithelium	Cylindrical epithelium	Subepithelium	Blood vessel endothelium	Inflammatory cells
CIN I	+++	++	-	-	++	+++
CIN II	++	++	+++	+	++	+++
CIN III	++	++	++	++	++	+++

Abbreviations in the Table: CIN – cervical intraepithelial neoplasia.

Table 3. IL-8 expression in different CIN stages

	Squamous epithelium	Subepithelium	Cylindrical epithelium	Subepithelium	Blood vessel endothelium	Inflammatory cells
CIN I	++	+	-	-	++	+
CIN II	++	+	+/++	++	++	++
CIN III	+	++	+	+	+++	+

Abbreviations in the Table: CIN – cervical intraepithelial neoplasia.

Table 4. IL-10 expression in different CIN stages

	Squamous epithelium	Subepithelium	Cylindrical epithelium	Subepithelium	Blood vessel endothelium	Inflammatory cells
CIN I	++	+	-	-	++	++
CIN II	++	+	++	++	++	+
CIN III	++	++	++	++	+++	+

Abbreviations in the Table: CIN – cervical intraepithelial neoplasia.

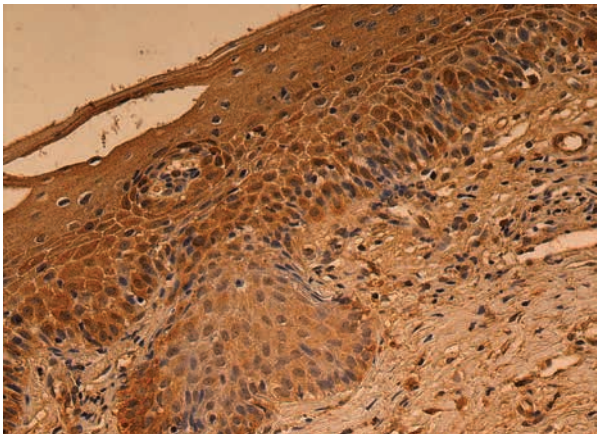

Fig. 1. Moderate number of IL-1α positive cells in epithelium and blood vessel endothelium in CIN III stage. (IL-1α IMH, x200)

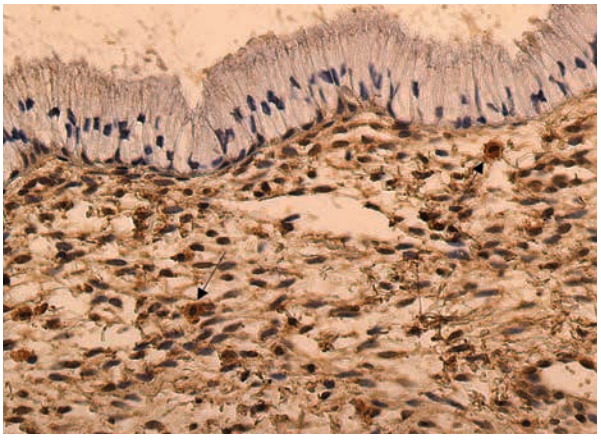

Fig. 2. A few IL-1α inflammatory cells in subepitjelium (arrows) of cervix uteri in CIN III stage. (IL-1α IMH, x200)

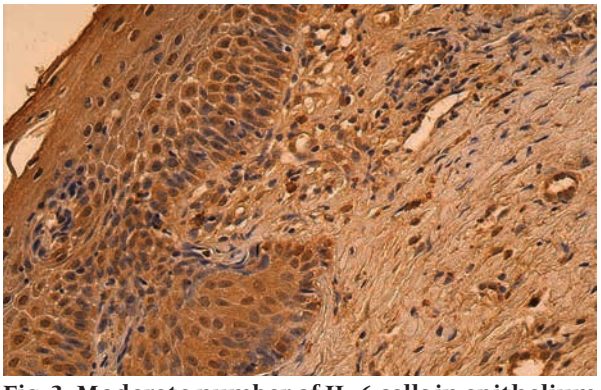

Fig. 3. Moderate number of IL-6 cells in epithelium and blood vessel endothelium in CIN III stage. (IL-6 IMH, x200)

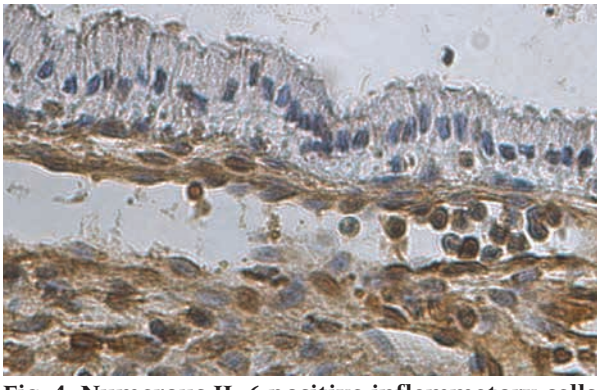

Fig. 4. Numerous IL-6 positive inflammatory cells in blood vessel and perivasculary in CIN III stage. (IL-6 IMH, x200)

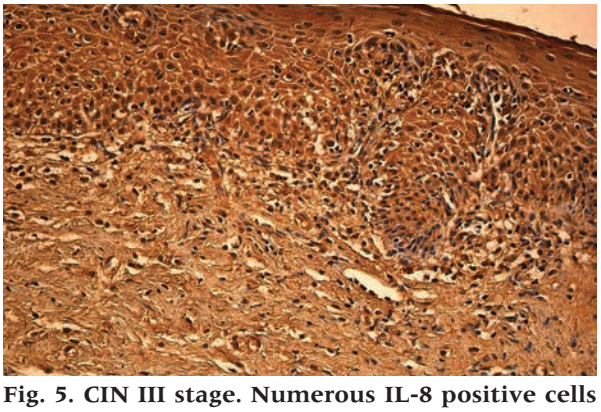

Fig. 5. CIN III stage. Numerous IL-8 positive cells in squamous epithelium. (IL-8 IMH, x200)

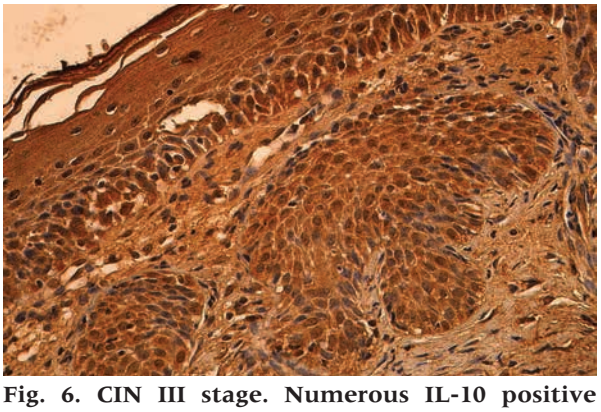

Fig. 6. CIN III stage. Numerous IL-10 positive epitheliocytes in squamous epithelium of cervix uteri. (IL-10 IMH, x200)

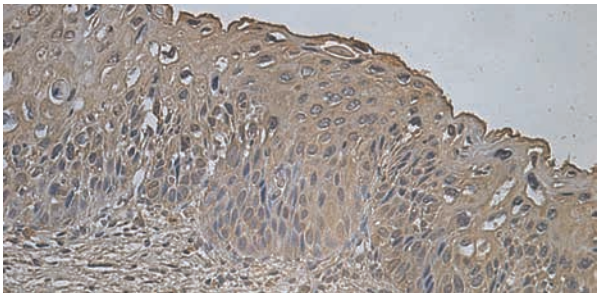

Fig. 7. CIN III stage. Weakly stained IL-10 positive cells in squamous epithelium, moderate number of IL-10 positive cells in stroma, especially in blood vessel endothelium and fibroblasts, but near absence of IL-10 positive inflammatory cells. (IL-10 IMH, x200)

DISCUSSION

Cervical cancer is one of the most common tumours found in working-age women causing health care expenditures and working-incapacity. Although there are many theories of CIN development, the full pathogenetic mechanism of the inflammatory reaction causing CIN changes remains unknown, one of the theories being cytokine imbalance. Our data indicates that there is a shift in local cytokine expression in both the epithelium and stroma in different CIN staging.

According to literature resources, and as proven by our study, the IL-1α expression tends to increase from CIN II to CIN III (7,18). However, some researchers say that HPV induces downregulation of IL-1 expression in mRNA and protein level (25), thus a decrease in IL-1α expression is expected, however this was not seen in our study as IL-1α expression increased from CIN II to CIN III, indicating that IL-1α is probably not as important and as predictable.

We found constant IL-6 expression in all three CIN stages, especially marked expression in inflammatory cells. Thus, it can be concluded that IL-6 is one of the main cytokines in tumour microenvironment development, as it promotes other cytokine expression and angiogenesis through IL-8 and VEGF (45,47). Production of IL-6 and IL-1 stimulate the production of Th17, which is said to be one of the main mechanisms of pathogenesis of HPV infection development into intraepithelial lesions (4,16). IL-6 mediates IL-8 expression (47). This explains why there is correlation between expression of IL-6 and IL-8 (48).

Opinions vary – whether the highest IL-8 expression is in HSIL (CIN II-CIN III) (7,23) or in LSIL (CIN I) where there is an active immune response (11,49). However, researchers agree that the expression is higher in CIN than in normal tissues (11,24,44,46). In our study, it was observed that IL-8 expression in squamous epithelium and inflammatory cells decreases trough CIN staging, but its expression in blood vessel endothelium and stroma increases. This suggests of possible microenvironment changes and hypoxia as tissue hypoxia and IL-8 expression is a linked process – less oxygen supplied to the tissues produces more IL-8 (27). The angiogenic activity of IL-8 promotes tumour growth (28,31). It is interesting that the removal of changed tissue reduces the IL-8 level, thus it can be concluded, that there is a direct correlation between affected keratinocytes and IL-8 expression (21,42). Hence, increased IL-8 expression in stroma may be indicative of neovascularization and faster tumour growth.

IL-10 – the only assessed anti-inflammatory cytokine in this study, inhibits the production of inflammatory cytokines and activates mast cells (33,38). It inhibits the production of IFN gamma, IL-1β and IL-6 by mononuclear phagocytes. It has an immunosuppressive action on Th1 cells and it enhances the activity of CD8+ lymphocytes (16,39). Thus, even if there are enough T lymphocytes in the neoplastic regions, IL-10 supresses their action (1,16). Thereby, it would be reasonable to expect a low expression of IL-10 in cervical tissues when there is a high pro-inflammatory cytokine expression and the other way around, but our study data contradicts literature sources. We found that IL-10 expression just like IL-6 expression remains the same trough all CIN stages except in inflammatory cells, where it decreases. The literature resources are inconclusive whether IL-10 expression in more pronounced in CIN I or CIN III. Some studies propose higher IL-10 expression is in CIN I compared to CIN II and CIN III (3,31), others advocate marked IL-10 expression in CIN II and CIN III compared to CIN I (5,8,9,35). Regarding the anti-inflammatory characteristics of IL-10, it is more believable that IL-6 acts as oncogenesis potentiating factor in CIN I and later on the expression of cytokines is just disrupted (32). However, some researchers state that IL-10 becomes a potent oncogenesis mediator (in autocrine pathway) by inactivating the Th1 immunity and activating Th2 immunity which favours further development of cervical intraepithelial lesions into squamous cancer (5). The second opinion is favoured by the fact that IL-10 is higher in immunosuppressed patients (3) and the HPV main target is to escape the immunity (17,20).

Our findings conclude that CIN is a very complex, neoplastic process and it is not reasonable to evaluate the effects of each cytokine individually, rather the balance and interactions of all the aforementioned cytokines should be observed as a whole. Understanding the molecular pathogenesis and its implications in the development of CIN could promote the rise of targeted treatment of CIN and *cervix uteri* cancer, which in turn would decrease the overall mortality and further increase the number of patients in whom initial CIN lesions regress back to normal epithelium.

CONCLUSIONS

IL-1α and IL-10 equal distribution in all CIN stages, suggests of pro- and anti-inflammatory cytokine balance in CIN development. IL-8 has the most variable expression, and the decrease in expression in CIN III stage indicates depletion of IL-8 production. IL-6 constant expression especially high expression in inflammatory cells, implies other cytokine production stimulation in all CIN stages and the lasting of chronic inflammation. Blood vessel endotheliocytes are cells which express cytokines the most, indicating an important role in CIN morfopathogenesis.

Conflict of interest: None

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