Low-grade Squamous Intraepithelial Lesion with *Chlamydia Trachomatis* Infection in Pap Smear: A Rare Association

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The role of Pap smear in detecting cervical carcinoma has been extensively acknowledged. However, it can also be very well utilized for detecting cervicovaginal infections such as fungi, bacteria, and parasites. Identifying these infections can help in providing immediate and correct treatment to the patient along with detection of any squamous intraepithelial abnormality, if present. *Chlamydia trachomatis* causes sexually transmitted disease along with cervical squamous dysplasia. However, as mentioned in literature, an association of chlamydial infection with squamous intraepithelial lesion is still not clear. Herein, we report a rare case of the low-grade squamous intraepithelial lesion along with chlamydial infection in the same patient.

**Keywords:** Cervicovaginal infections, Chlamydia, Pap smear, Squamous dysplasia

INTRODUCTION

Pap smear examination is commonly employed as a primary screening test for detection of the cervical intraepithelial lesion or cervical carcinoma. It can also be very well utilized for detecting genital infections. Few organisms detected on routine Pap smears may be very rare and can be associated with low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion and hence should be reported correctly to provide timely intervention and prevent unnecessary treatment. Herein, we report a rare association of chlamydial infection with LSIL. Various studies in literature have shown both, positive and negative correlation of chlamydial infection with cervical intraepithelial neoplasia (CIN).¹⁻⁸

CASE REPORT

A 42-year-old female patient was referred to gynecology department with complaints of dysfunctional uterine bleeding and vaginal discharge. She was parity 3 with 3 living healthy children. She did not have any other clinical problems or other chronic illness. Routine laboratory parameters such as peripheral smear and complete blood count were within normal limits. She underwent routine Pap smear examination. The smear was satisfactory for evaluation comprising predominantly of superficial, intermediate, and few parabasal cells. Many of the mature squamous cells showed enlarged hyperchromatic nuclei with moderate anisonucleosis, irregular nuclear membrane, and perinuclear clearing, suggestive of LSIL (Figure 1a and b). Few binucleated and multinucleated cells were also noted (Figure 2).

Few cells showed intracytoplasmic coccoid bodies with a clear halo and vacuolated cytoplasm consistent with elementary bodies of *Chlamydia trachomatis* (CT) (Figure 3a and b). Large cytoplasmic inclusions with eosinophilic center were also noted in squamous cells (Figure 4a and b). Endocervical cells were not seen. Background showed moderate inflammation.

Various causes of cytoplasmic vacuolation, such as cryosurgery, radiotherapy, and chemotherapy, were ruled out in this patient. The diagnosis was confirmed with serological techniques, and the partner was advised to undergo screening. Finally, an impression of LSIL with coexisting chlamydia infection was made.

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DISCUSSION

Cervicovaginal infections are caused by bacteria, fungi, or parasites. Although Pap smear is employed as a quick screening test for detection of cervical dysplasia or carcinoma, it can also be a very simple, easier, and cheaper technique to screen genital infections in the patients who come to gynecology department for other complaints such as discharge per vaginum and dyspareunia. In this way, sometimes, rare organisms can be identified which require a specific mode of treatment and hence such organisms should be reported correctly and timely so that patients get proper intervention. Sullam et al., in his study reported a very low prevalence rate for CT infection (4.2%).

Cervical carcinoma is a very common malignancy, especially in India and human papilloma virus (HPV - 16 and 18) has been associated with its genesis. However, it is not necessary that every woman with HPV infection will develop cervical neoplasia. In different studies, it is proposed that apart from HPV infection, various other cofactors are involved in its causation (Figure 5).

It is well known that CT infection is one of the common sexually transmitted diseases (STDs). In women, it causes mucopurulent cervicitis, urethritis, salpingitis, and very importantly, it affects newborns too. Infertility has also been related to this particular infection along with other pregnancy-related complications such as premature rupture of fetal membranes, premature delivery, and postpartum endometritis. In studies, it has also been reported to be associated with follicular cervicitis and carcinoma in situ. A very simple flowchart depicts the role of CT infection in genesis of cervical dysplasia or cancer (Figure 6).

Cytomorphologically, cells infected with CT are large, atypical metaplastic cells with vacuolated cytoplasm, harboring coccoid bodies, or inclusion bodies of the organism in different phases of their development. In a study by Gupta et al., various stages of CT infection were elaborated. Their development has been divided into 3 stages:

Figure 1: (a and b) Mature squamous cells showed enlarged hyperchromatic nuclei with moderate anisonucleosis, irregular nuclear membrane, and perinuclear clearing (low-grade squamous intraepithelial lesion) (Pap x400)

Figure 2: Few binucleated and multinucleated mature squamous cells of low-grade intraepithelial lesion (Pap x400)

Figure 3: (a and b) Intracytoplasmic coccoid bodies with a clear halo and vacuolated cytoplasm consistent with elementary bodies of Chlamydia trachomatis (Pap x400, x1000)

Figure 4: (a and b) Large cytoplasmic inclusions with eosinophilic center were also noted in squamous cells (non-infectious forms) (Pap x400)
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1. First being the fine acidophilic coccoid bodies (primary elementary bodies). This is the infective stage.
2. The above stage is followed by localization, condensation, and transformation of these bodies into fine perinuclear vacuoles containing fine eosinophilic/basophilic granular bodies. This stage is non-infectious.
3. In the final stage, large intracytoplasmic vacuoles are formed that contain either a central homogeneous condensed area surrounded by a halo or densely packed coccoid structures diffusely distributed throughout the vacuole.

In our case, both the infectious stage (elementary bodies) and non-infectious stage were noted. However, before reporting such infections, various causes of cytoplasmic vacuolation should be ruled out such as patients on radiotherapy, chemotherapy, and cryosurgery, as done in the present case. The presence of condensed mucus secretion and coccoid bacteria in these cytoplasmic vacuolation should be cautiously observed and reported to avoid misdiagnosis. In such conditions, confirmatory tests should be undertaken, such as culture using McCoy cells, immunofluorescence using monoclonal antibody, enzyme-linked immunosorbent assay, and polymerase chain reaction, as confirmed by culture in the present case. It is also important to advise for the screening of the partner for any such abnormality.

Various studies have given both positive and negative results for its association with cervical cancer. The risk of squamous cell carcinoma is increased with coinfection with chlamydia, as stated in studies by Madeleine et al., and Smith et al. It was also noted in studies by Gopalkrishna et al., and Lehman et al., that HPV-positive samples had a higher prevalence of CT infection when compared to HPV-negative samples. However, overall its association give a mixed results, as noted in other studies, e.g., Castle et al., and de Paula et al., showed no association of chlamydia with CIN or cervical carcinoma in their studies.

The important point is to report such rare organisms in Pap smear as CT infection can be easily treated and complications can be prevented, thereby curtailing the development of cervical neoplasia. Chakrabarti et al., reported that CT infection is the most common organisms associated with CIN. Chlamydial infection is also associated with eight-fold increase in the risk of having an unhealthy cervix. However, Bhatla et al., in his study showed no association among chlamydia, HPV, and development of CIN in hospital-based symptomatic patients. It was also concluded in their study that more studies should be done enrolling younger women to exactly state whether CT infection which was acquired in younger age promoted persistence of HPV infection and further progression to chlamydial infection or not.

**CONCLUSION**

The detection of CT organism in Pap smear is very rare, and various studies have shown different results explaining its association with LSIL. However, it should be cautiously reported, as it is of paramount public health importance. It is one of the common causes of STDs and also can be easily treated if reported immediately with such an easy and simple method of the screening tool, Pap smear. In this manner, prompt treatment can be given to the patient for both cervical dysplasia and concurrent chlamydial infection. This rare case report highlights the importance of cytomorphological features in correct interpretation and diagnosis of LSIL and CT. Hence, further studies are invited to establish or justify the role of chlamydia in the genesis of cervical dysplasia or carcinoma.
REFERENCES


