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Assessment of the Association of Vaginal Infection with Atypical Pap-smear Results

Vajinal İnfeksiyon ile Atipik Pap-smear Sonuçları Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Introduction: *This study aims to evaluate the frequency of infectious agents in Pap-smear results and their association with pathological results.*

Materials and Methods: *This retrospective study was conducted by evaluating the smear results between January 1, 2021 and December 31, 2021 at the Tuzla State Hospital. Smear results were classified according to the Bethesda system [normal, atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells-high-grade (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC) carcinoma]. In addition, vaginitis agents (Trichomonas vaginalis, Gardnerella vaginalis, Candida spp., Actinomyces spp.) found in the report were also recorded separately.*

Results: *In the study, as a result of the evaluation of 4708 smear results, a vaginal infectious agent was found in 675 patients (16.55%). G. vaginalis was observed most frequently in 322 patients (7.9%), and the Candida spp. was observed in 298 patients (7.3%). Actinomyces spp. was observed in eight patients and T. vaginalis was observed in two patients. Pathology results were normal in 4129 (87.7%) according to the 2014 Bethesda system. Five hundred and fifty (11.68%) of them were ASC-US, nine (0.19%) ASC-H, 17 (0.36%) LSIL, and three (0.06%) were reported as HSIL. G. vaginalis was accompanied in 29 of the ASC-US results, and Candida spp. accompanied 10. Candida spp. was observed in 2 of 9 patients diagnosed with ASC-H, and G. vaginalis was observed in one of them. G. vaginalis was found in 1 of 17 patients diagnosed with LSIL, and no infection was found in three patients diagnosed with HSIL.*

Conclusion: *Routine Pap-smear examination is essential for identifying cervicovaginal infectious agents as well as cervical pathologies.*

Key Words: *Papanicolaou smear; Vaginitis; Ascus; Cervical pathology; Pap-smear*

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ÖZ

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Giriş: *Bu çalışmanın amacı Pap-smear sonuçlarında infeksiyon faktörlerinin sıklığını ve patolojik sonuçlarla ilişkisini değerlendirmektir.*

Materyal ve Metod: *Bu retrospektif çalışma, 1 Ocak 2021 ve 31 Aralık 2021 tarihleri arasında Tuzla Devlet Hastanesinde smear sonuçları değerlendirilerek yapılmıştır. Smear sonuçları Bethesda sistemine göre sınıflandırılmıştır [normal, önemi belirsiz atipik skuamöz hücreler (ASC-US), yüksek dereceli atipik skuamöz hücreler (ASC-H), düşük dereceli skuamöz intraepitelyal lezyon (LSIL), yüksek dereceli skuamöz intraepitelyal lezyon (HSIL), atipik glandüler hücreler (AGC), karsinom]. Ayrıca raporda bulunan vajinit ajanları da (Trichomonas vaginalis, Gardnerella vaginalis, Candida spp., Actinomyces spp.) ayrıca kayıt altına alınmıştır.*

Bulgular: *Çalışmada 4708 smear sonucunun değerlendirilmesi sonucunda 675 hastada (%16.55) vajinal infeksiyon faktörü saptandı. En sık olarak 322 hastada (%7.9) G. vaginalis, 298 hastada (%7.3) Candida spp. gözlendi. Sekiz hastada Actinomyces spp., iki hastada T. vaginalis görüldü. 2014 Bethesda sistemine göre 4129 (%87.7) hastada patoloji sonuçları normaldi. Bunların 550'si (%11.68) ASC-US, dokuzu (%0.19) ASC-H, 17'si (%0.36) LGSIL, üçü (%0.06) HSIL olarak rapor edildi. ASC-US sonuçlarının 29'una G. vaginalis, 10'una Candida spp. eşlik etti. ASC-H tanısı alan dokuz hastanın ikisinde Candida spp., birinde G. vaginalis görüldü. LGSIL tanısı alan 17 hastanın birinde G. vaginalis saptanırken, HSIL tanısı alan üç hastada infeksiyon saptanmadı.*

Sonuç: *Rutin Pap-smear incelemesi, servikovajinal infeksiyon etkenlerinin belirlenmesinde ve servikal patolojilerin saptanmasında önemli bir yere sahiptir.*

Anahtar Kelimeler: *Papanicolaou smear; Vajinit; Ascus; Servikal patoloji; Pap smear*

INTRODUCTION

The Pap-smear test is the most widely used screening method for cervical cancer and its precursor lesions[1]. The pap smear test can also detect some viral, bacterial, and fungal infections of the cervix and vagina[2]. The Bethesda system was first defined in 1989 by the American National Cancer Institute (NCI). This reporting system provides a better evaluation of the cytopathological findings of cervicovaginal smears and a common language in terminology[3]. Microorganisms are reported in five categories in cervical cytology in the Bethesda system. These categories are *Trichomonas vaginalis*, fungal organisms morphologically composed of *Candida* species (spp.), the shift of flora towards bacterial vaginosis (*Gardnerella vaginalis*), bacterial morphology consisting of *Actinomyces* spp., and cellular changes caused by Herpes simplex virus[1]. According to the revised 2014 Bethesda System, the report includes sample type, sample adequacy, general classification, additional tests [e.g. (*Human Papilloma Virus* (HPV) DNA], comments/results, and recommendations. It is also recommended to report the presence of endometrial cells and benign changes including specific infections[3,4].

Changes in vaginal microbiological flora and inflammation can help in the acquisition and transmission of HPV infection, which is the main cause of cervical cancer. Inflammation of the cervix destroys the cervical epithelium, helping HPV to enter the actively proliferating basal cells of the cervical epithelium[5]. Inflammation causes DNA damage in the host cell, resulting in the integration of viral DNA. As a result, HPV infection gradually progresses to micro-invasion and invasive cervical cancer[6].

This study aims to evaluate the presence of infectious agents in atypical smear results.

MATERIALS and METHODS

In the study, results of Pap-smear tests sampled by Tuzla State Hospital Gynecology and Obstetrics Clinic between January 1, 2021 and December 31, 2021 and evaluated in the pathology laboratory were obtained from the hospital database and analyzed retrospectively. The study was approved by the Marmara University Faculty

of Medicine Ethics Committee (Decision no: 09.2022.46), and the study was designed in accordance with the Helsinki Declaration.

In this study, a total of 5215 smear results were evaluated. 4708 smear results that met the criteria were used for the analysis. Smear results of patients who are sexually active, over the age of 21, and have not had any other smear test in the last three years were included in the study. Repeated smear results from the same patient, smear results of patients with a known history of gynecological malignancy, vaginal cuff smear results from hysterectomized patients, and insufficient smear results were not included in the study.

Samples were taken from each patient included in the study with a cervibrush on the gynecological table, sent to the pathology laboratory with thin-prep liquid-based solution, and classified according to the 2014 Bethesda system by pathology specialists (Normal, Atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells-high-grade (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), adenocarcinoma and squamous cell carcinoma). In addition, reported vaginitis agents (*T. vaginalis*, *G. vaginalis*, *Candida* spp., *Actinomyces* spp.) were also recorded separately.

Statistical Analysis

The data were entered in MS Excel 2016 and then analyzed statistically. The values are presented as the number (%).

RESULTS

In the study, a total of 4708 smear results from patients that met the inclusion criteria were evaluated. Of these results, 4129 (87.7%) were normal, 550 (11.68%) were ASC-US, nine (0.19%) were ASC-H, 17 (0.36%) were LSIL, three (0.06%) were reported as HSIL and no AGC or squamous/adenocarcinoma was reported (Table 1).

Infectious agents were reported in the smear results of 675 (16.55%) patients in the study: *T. vaginalis* was reported in two (0.05%) patients, *Actinomyces* spp. in eight (0.2%) patients, fungal organisms compatible with *Candida* spp. in 298 (7.31%) patients, and *G. vaginalis* in 322 (7.9%) patients (Table 1).

When the infectious agents accompanying Bethesda smear result categories are examined, no infectious agent was observed in those with HSIL. *G. vaginalis* was observed in 1 of 17 patients diagnosed with LSIL. While no infectious agent was observed in 6 of 9 patients diagnosed with ASC-H, *Candida* spp. was observed in two, and *G. vaginalis* in one patient. The most common abnormal cytology result accompanied by infection was ASC-US. In the study, 511 of 550 ASC-US cases were normal, 29 had *G. vaginalis* and 10 had *Candida* spp. In cases reported as normal, 291 *G. vaginalis*, 286 *Candida* spp., eight *Actinomyces* spp., and two *T. vaginalis* agents were observed (Table 1).

Table 1. Evaluation of infectious agents and cervical pathologies

	T. vaginalis	*Actinomyces* spp.	*Candida* spp.	*G. vaginalis*	Normal	Total*
HSIL	0	0	0	0	3	3 (0.06)
LSIL	0	0	0	1	16	17 (0.36)
ASC-H	0	0	2	1	6	9 (0.19)
ASC-US	0	0	10	29	511	550 (11.68)
Normal	2	8	286	291	3542	4129 (87.70)
Total*	2 (0.04)	8 (0.17)	298 (6.33)	322 (6.83)	4078 (86.62)	4708

Note: *Total group was expressed as patients (%).
ASC-US: Atypical squamous cells of undetermined significance, ASC-H: Atypical squamous cells-high grade, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion.

DISCUSSION

Cervical cancer is the fourth most common cancer in women worldwide, after breast cancer, colorectal cancer, and lung cancer. According to the results of the GLOBOCAN 2020 database, in developing countries including Türkiye, cervical cancer ranks second after breast cancer in women in terms of age-standardized incidence and death rates (18.8 new cases per 100.000 people and 12.4 deaths per 100.000 people) [7,8]. Cervical cancer is a preventable cancer type whose etiopathogenesis has been well-defined[9]. George Papanicolaou performed the first cytological examination of the cervix in the 1940s, and the presence of abnormal cells in the cervix of women can be detected years before the diagnosis of cervical cancer. This test is known as a Papanicolaou smear or Pap-smear test[10].

This study aims to evaluate the frequency of infectious agents and their associations with pathologies in Pap-smear results used in cervical cancer screening. In the study, as a result of the evaluation of 4708 smear results, an infectious agent was found in 675 patients (13.38%). *G. vaginalis* was found most frequently in 322 patients (6.83%), and *Candida* spp. were observed in 298 patients (6.33%). *Actinomyces spp.* were observed in eight patients (%0.17) and *T. vaginalis* was observed in two patients (%0.04).

In the study, ASC-US was observed in 550 cases (%11.68), 29 of them were accompanied by *G. vaginalis*, and 10 of them were accompanied by *Candida* spp. Two out of nine patients with ASC-H had *Candida* spp. infection and one patient with ASC-H had *G. vaginalis*. *G. Vaginalis* accompanied 1 out of 17 LSIL cases, while no infectious agent was found in any of the three HSIL cases.

In a study conducted in the Eastern Black Sea region in 2014 by Tekin et al.[11], which included 12.558 cases, abnormal Pap-smear results were reported as 56.1% ASC-US, 2.5% ASC-H, 17.5% LSIL, 7.9% HSIL, % 15.3 AGC.

In the literature, the rate of infection with *T. vaginalis* varies between 10-90%[12,13]. Rassjo et al.[14] reported a rate of 8.0% using the polymerase chain reaction method in Kampala, and Chakraborty et al.[15] 34% by culture method, Klinger et al.[16] reported a rate of 10.7%. Malkavi et al.[17] examined cervical smear samples of 1176 cases and reported *Candida* albicans in 1.2%, *T. vaginalis* in 0.9% and *Actinomyces* spp. in one case. The results obtained by different researchers were found to be similar.

Unalan et al.[18] reported normal lesions in 61.6%, atrophy in 6.1%, inflammation in 8.4%, bacteria in 4.6%, candidiasis in 1.5%, and precancerous lesions in 0.2% of 571 cases. In a study conducted in Ankara Etlik Zübeyde Hanım Gynecology and Obstetrics Training and Research Hospital, 50.6% infection (*G. vaginalis*, *Candida* spp, *T. Vaginalis*...), 21.6% inflammation, 1.7% atrophy, and 0.2% precancerous lesions were found in 3013 cases[19]. In the study conducted by Karcı et al., in which 1191 smear samples were examined, the incidence of *Candida* spp. was reported as 4.8%, bacterial vaginosis as 7.1%, and *T. vaginalis* as 0.3%[20]. In the study by Koşar Can et al., which included 9982 patients, inflammation was found in 3715 (37.21%) patients, candidiasis in 104 patients (1.04%), bacterial vaginosis in 228 patients (2.28%), and atrophy in 842 patients (8.43%)[10].

In a study investigating the frequency of vaginitis in Pap-smear samples in Iran, Maria et al. reported that the most common pathogen was *Candida* spp., followed by *T. vaginalis* and *G. vaginalis*[21]. Other studies found that the prevalence of *Candida spp.* was 25.2%, the rate of *T. vaginalis* was 1.37%, and 25% for *G. vaginalis*[22,23]. Different study populations, various climatic, socioeconomic, and cultural conditions, different sensitivity of diagnostic tests, and the use of different diagnostic methods were found to be the causes of the different infection rates[22,24].

Although the percentages vary in general studies, infectious agents are shown in the Pap-smear test. In our current study, there are values similar to previous studies. The presence of infectious agents causes epithelial damage and causes changes in Pap-smear results[23].

The most important result of the study is that one of the underlying causes of ASC-US results, which is the most common pathology in smear results, is its frequent association with infection. Abnormalities in pathology results cause anxiety in patients. However, the patient's anxiety should be alleviated by explaining that this pathological result is most likely due to infection, appropriate treatment should be administered, and the patient should be rechecked with a smear test after treatment. As a limitation of the study, predisposing factors such as vaginal douching, polygamy, smoking, use of immunosuppressive drugs, and chronic disease, which would increase the occurrence of infection, could not be evaluated, because they were not reported regularly in the hospital database for every patient.

CONCLUSION

Routine Pap-smear examination plays an important role in detecting infections in most women. Pap-smear screening can be helpful in the early diagnosis of a pathological or infective condition, helping to initiate appropriate treatment and prevent further complications.

ETHICS COMMITTEE APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Marmara University (Decision no: 09.2022.46)

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: MMK

Analysis/Interpretation: MMK

Data Collection or Processing: OSS, BNAH

Writing: MMK, OSS

Review and Correction: MMK, BNAH

Final Approval: MMK

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