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Prevalence of high-risk human papilloma virus infection and cervical cytological abnormalities in female Turkish patients with rheumatologic disease

Cem Yalçınkaya [1], İbrahim Kale [2], Özlem Pehlivan [3]

[1] Umraniye Training and Research Hospital, Department of Gynecological Oncology, Istanbul, Turkey
[2] Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey
[3] Umraniye Training and Research Hospital, Department of Rheumatology, Istanbul, Turkey

ORCID ID of the author(s)
CY: 0000-0001-7533-0838
İK: 0000-0001-7802-7199
ÖP: 0000-0002-6887-1801

Corresponding Author
İbrahim Kale
Merdivenköy Mahallesi, Nazenin Sokak. Apartman no: 9 Kat: 13 Daire: 34 Kadıköy, Istanbul, Turkey
E-mail: dribakale@hotmail.com

Ethics Committee Approval
The Local Ethics Committee of Umraniye Training and Research Hospital, Istanbul, Turkey have approved this study (Ethics Committee Approval No: B.10.1.TKH.4.34.H.GP.0.01/254). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: It is believed that patients with rheumatological diseases (RDs) are more prone to infectious diseases, possibly due to both disease-related immune dysfunction and chronic inflammation, and immunosuppressive agents used in the treatment of rheumatological diseases. In this context, we aimed to evaluate the prevalence of high-risk human papillomavirus (Hr-HPV) infection and cervical cytological abnormalities in Turkish female patients with RDs and compare them with healthy controls (HCs).

Methods: 362 sexually active patients with RDs followed up between January 2014 and June 2021 were included in this cross-sectional study. Patients with RDs were classified as autoimmune and non-autoimmune groups according to seropositivity. Data of 883 age-matched HCs were used for comparison. Demographic features, cervical cytology reports of the patients and HPV test results were retrieved from hospital database. Cervical cytological abnormalities was categorized according to Bethesda 2014. Cobas assay was used for detecting and typing for Hr-HPV.

Results: The RDs group and the HCs group were similar in terms of mean age, BMI, and rate of smokers (P>0.05). Cytological evaluation was carried out in all of 362 patients with RDs (161 autoimmune and 201 non-autoimmune) and in all of 883 HCs. HPV test was applied in 286 patients with RDs and 776 of HCs. 16 (4.4%) patients with RDs and 58 (6.6%) HCs had cervical cytological abnormality. Of the patients who underwent HPV testing; 22 (7.7%) patients with RDs and 75 (9.7%) HCs had Hr-HPV. The prevalence of cervical cytologic abnormalities and Hr-HPV infection rate were similar between patient groups and HCs (P=0.186 and P=0.400, respectively).

Conclusion: It was determined that chronic systemic inflammation, which plays a role in the pathogenesis of rheumatological diseases, and immunosuppressive agents used in the treatment did not increase the prevalence of Hr-HPV infection and cervical cytological abnormalities.

Keywords: Cervix uteri, Papanicolaou test, Papillomaviridae, Rheumatologic disease

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Introduction

Human papillomavirus (HPV) infection is known as the main cause of cervical premalignant lesions and cervical cancer [1]. Persistent infection with high-risk HPV (Hr-HPV) types, especially type 16 and 18, are significantly associated with cervical cancer [2]. While most HPV infections are cleared by the individual's immune system within a few years, persistent infections can lead to precancerous and invasive lesions [3].

Cervical cancer screening can be done only with Pap smear test or HPV test or with co-test in which both cervical cytological evaluation and HPV are examined together. The Bethesda system is commonly used for reporting cervical cytological abnormalities [4]. Cytological abnormality and/or HPV positivity may require colposcopic examination and biopsy [5].

Rheumatologic diseases (RDs) include a wide spectrum of disorders causing chronic inflammation affecting the joints and/or organ systems [6]. Corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) or immunosuppressives are frequently used for treatment of RDs [7]. Because HPV infection is controlled by both local and systemic immunity, immunocompromised individuals are thought to be more likely to have HPV infection and persistence [8].

Some studies demonstrated that patients with autoimmune disease such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), were found to be more likely to have abnormal cervical cytology and high prevalence of HPV infection [9, 10]. However, prevalence of cervical cytological abnormalities and HPV infection among other RDs, especially in patients with non-autoimmune rheumatologic diseases, are scarce.

The aim of our study was to assess the prevalence of Hr-HPV infection and cervical cytological abnormalities in Turkish female patients with different RDs including autoimmune and non-autoimmune spectrum, and compare them with a healthy control group.

Materials and methods

This retrospective, cross-sectional study was conducted in Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey. The study group consisted of 362 sexually active female patients with RDs who applied to the outpatient clinic for routine gynecological care between January 2014 and June 2021 and had Pap smears. Study patients were divided into two groups as autoimmune RDs and non-autoimmune RDs. Patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), dermatomyositis (DM), antiphospholipid syndrome (APS), Sjogren's syndrome and granulomatosis with poliangiitis (Wegener's) were classified as autoimmune inflammatory RDs (seropositive) group (n=161). Patients with ankylosing spondylitis and other seronegative spondyloarthropathies, psoriatic arthritis, Behçet's Disease, familial mediterranean fever (FMF), gout, seronegative arthritis and osteoarthrosis were classified as non-autoimmune (seronegative) group (n=201).

The control group consisted of 883 randomly selected, age-matched women who underwent cervical screening during the study period, who had not any of the following; known previous cervical cytological anomaly, HPV positivity, history of any cancer, rheumatological disease and history of immunosuppressive therapy or steroid use.

HPV Testing and Cervico-vaginal Cytology

Pap smear test and cytological evaluation was performed on all participants. Cervical cytology samples of patients with RDs and age-matched HCs were taken by gynecologist and collected in ThinPrep® PreservCyt® Solution (Hologic Inc., Marlborough, MA) and then sent to the pathology unit specialized in processing cervical cytology samples. Samples were examined by these experienced pathologists for cytological abnormalities and tested for HPV.

The cytology diagnoses were graded according to the 2014 Bethesda classification [11]. In this study, we classified those with cervical cytology results reported as atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) as low-grade disease (LSIL). We classified as high-grade disease (HSIL) those reported as a high-grade squamous intraepithelial lesion (HSIL) or atypical squamous cells cannot exclude HSIL (ASC-H) or atypical glandular cells (AGC) as a result of cervical cytology. Smears without any signs of significant abnormalities categorized as negative for intraepithelial lesion and malignancy (NILM).

HPV testing was performed by using the Cobas® Human Papilloma Virus Test System (Roche Molecular Systems, Branchburg, NJ, USA) to detect the 14 high-risk HPV types. The Cobas HPV testing system is a fully automated PCR-based HPV test that analyzes HPV DNA from cervical specimens collected in liquid-based cytology medium [12]. This system is one of five approved HPV test by the US Food and Drug Administration for HPV DNA typing [13]. The Cobas HPV test can separately report HPV 16 and 18, while a pooled test result of 12 other HR-HPV types together (31,33,35,39,45,51,52,56,58,59,66,68) [14].

Statistical analysis

Statistical analysis of the study was performed using SPSS 16.0 software (SPSS INC., Chicago, Il, USA). Quantitative data were expressed as mean (SD). Categorical data were described as percentages and numbers, and tested by using Pearson Chi square test or Fisher's exact test. $P<0.05$ was considered statistically significant.

Results

A total of 362 patients with RDs (mean age 37.6 (7.7) years) and 883 age-matched HCs (mean age 38.5 (5.5) years) were included in this study. In the RDs group, mean BMI was 26.87 kg/m^2 and smoking rate was 19.9%. In the HCs group, the mean BMI was 27.13 kg/m^2 and the smoking rate was 19.2%. The RDs group and the HCs group were similar in terms of mean age, BMI, and rate of smokers ($P=0.256$, $P=0.457$, $P=0.725$, respectively) (Table 1).

The distribution of cytologic abnormalities and HPV testing among patients with RDs were summarized in Table 2.

Table 1: Comparison of demographic characteristics of patients with RDs and HCs

	Patients with RDs n=362	Healthy Controls n=883	*P*-value
Age (years)	37.6 (7.7)	38.5 (5.5)	0.256
BMI (kg/m2)	26.87 (5.67)	27.13 (4.64)	0.457
Smoking			
Yes	72 (19.9%)	168 (19.2%)	0.725
No	290 (80.1%)	715 (80.9%)	

Table 2: The distribution of cytologic abnormalities and HPV testing among patients with RDs

	Autoimmune Group						Non- Autoimmune Group						
	RA (n=78)	SLE (n=22)	SSc/DM (n=13/1)	APL (n=5)	Sjögren (n=40)	GPA (n=2)	AS (n=21)	SpA (n=33)	PSA (n=14)	Behcet (n=30)	FMF (n=57)	Seronegative Arthritis (n=43)	Gout/OA (n=2/1)
LSIL	2	0	0	0	1	1	1	1	1	1	3	2	0
HSIL	0	0	1	0	0	0	1	0	1	0	0	0	0
NILM	76	22	13	5	39	1	19	32	12	29	54	41	3
HPV positive	4	2	1	0	1	1	4	0	1	2	4	2	0
HPV 16	0	0	0	0	0	0	3	0	0	0	1	0	0
HPV18	0	1	0	0	0	0	0	0	0	0	0	0	0
HPV others	4	1	1	0	1	1	1	0	1	2	3	2	0
HPV negative	58	16	11	3	26	1	15	29	12	22	39	29	3

RA: Rheumatoid Arthritis, SLE: Systemic Lupus Erythematosus, SSc: Systemic Sclerosis, DM: Dermatomyositis, APL: Antiphospholipid Syndrome, GPA: Granulomatosis with Polyangitis, AS: Ankylosing Spondylitis, SpA: Spondyloarthritis, PSA: Psoriatic Arthritis, FMF: Familial Mediterranean Fever, OA: Osteoarthritis, LSIL: Low Grade Squamous Intraepithelial Lesion, HSIL: High Grade Squamous Intraepithelial Lesion, NILM: Negative for Intraepithelial Lesion and Malignancy

Prevalence of cervical cytological abnormality

Among patients with RDs, 346 (95.6%) patients did not have malignancy or intraepithelial lesions, while 16 (4.4%) had cytological abnormalities (13 LSIL and 3 HSIL). Among HCs, 58 (6.6%) individuals were found to have cytological abnormalities (47 LSIL and 11 HSIL). The prevalence of cervical cytological abnormalities were similar between patients with RDs and HCs (P=0.186) (Table 3).

Table 3: The prevalence of cytological abnormalities between patients with RDs and HCs

Cytology	Patients with RDs n=362	Healthy Controls n=883	*P*-value
LSIL+HSIL n (%)	16 (4.4)	58 (6.6)	0.186
NILM n (%)	346 (95.6)	825 (93.4)	

LSIL: Low Grade Squamous Intraepithelial Lesion, HSIL: High Grade Squamous Intraepithelial Lesion, NILM: Negative for Intraepithelial Lesion and Malignancy

When autoimmune RDs, non-autoimmune RDs and control group were compared in terms of the cervical cytological abnormalities, five patients (3.1%) were found in the autoimmune and 11 (5.5%) in the non-autoimmune group. The prevalence of cervical cytological abnormalities were similar between autoimmune group, non-autoimmune group and HCs (P=0.221) (Table 4).

Prevalence of Hr-HPV

Of 362 patients with RDs, 286 had HPV testing and 22 (7.7%) had Hr-HPV. HPV 16 was detected in four patients, HPV 18 was detected in one patient, and other Hr-HPVs were detected in 17 patients. HPV testing was performed in 776 of 883 women in the control group, and Hr-HPV was detected in 75 (9.7%) of them. Of these, 14 had HPV 16, 5 had HPV 18 and 56 had other Hr-HPV. The prevalence of Hr-HPV was not statistically different between patients with RDs and HCs (P=0.400) (Table 5).

Table 4: The prevalence of cytological abnormalities between patient groups and HCs

Cytology	Autoimmune Group n=161	Non-Autoimmune Group n=201	Healthy Controls n=883	*P*-value*	*P*-value **
LSIL+HSIL n (%)	5 (3.1)	11 (5.5)	58 (6.6)	0.314	0.221
NILM n (%)	156 (96.9)	190 (94.5)	825 (93.4)		

* comparison between autoimmune vs non-autoimmune groups, ** comparison between all groups, LSIL: Low Grade Squamous Intraepithelial Lesion, HSIL: High Grade Squamous Intraepithelial Lesion, NILM: Negative for Intraepithelial Lesion and Malignancy

Table 5: The Prevalence of Hr-HPV between patients with RDs and HCs

Hr-HPV	Patients with RDs n=286	Healthy Controls n=776	*P*-value
Positive n (%)	22 (7.7)	75 (9.7)	0.400
Negative n (%)	264 (92.3)	701 (90.3)	

Of 22 RDs with Hr-HPV positivity, 9 (7.3%) (one patient HPV 18, and 8 other Hr-HPV) were in the autoimmune group and 13 (8.0%) (four patients HPV 16, and 9 other Hr-HPV) were in the non-autoimmune group. Autoimmune RDs, non-autoimmune RDs and control group were also compared in terms of HPV positivity. The prevalence of Hr-HPV was similar between three groups (P=0.598) (Table 6).

Table 6: The Prevalence of Hr-HPV between patient groups and HCs

Hr-HPV	Autoimmune Group n=124	Non-Autoimmune Group n=162	Healthy Controls n=776	*P*-value*	*P*-value **
Positive n (%)	9 (7.3)	13 (8.0)	75 (9.7)	1.000	0.598
Negative n (%)	115 (92.7)	149 (92.0)	701 (90.3)		

* comparison between autoimmune vs. non-autoimmune groups, ** comparison between all groups

Discussion

In this study, we could not find a statistical difference in the prevalence of cervical cytological abnormalities and Hr-HPV positivity between the patient group with rheumatological diseases and the age-matched healthy control group.

The third most common genital cancer in Turkish women is cervical cancer with an average incidence of 4.42 per 100,000 women [15]. There are different study results in the literature about Hr-HPV prevalence in Turkish population. In a study by Demir et al. [16] in which patients with normal cervical cytology were evaluated, the prevalence of HPV was found to be 17.9%. In a hospital based study conducted by Yuce et al. [17] the prevalence of high-risk HPV was 25.7%. In another study of Polat et al. [18] the prevalence of both Hr-HPV and abnormal cervical cytology were found to be 23%. Unlike the studies mentioned above, the prevalence of Hr-HPV in the healthy control group was found to be lower than the general average of the Turkish population in our study (9.7%).

Most of the studies investigating the prevalence of HPV and cervical cytological abnormalities in rheumatologic patients in the literature were conducted with SLE patients. In a study of 32 SLE female patients and controls, Al-Sherbeni et al. [19] found that there is a predisposition to cervical atypia in SLE women. In another study by Nath et al. [10] in which Pap smears of 30 female SLE patients and healthy controls were evaluated. The prevalence of abnormal Pap smear findings and the prevalence of Hr-HPV in female SLE patients was significantly higher than in healthy controls. Tam et al. [20] reported that cervical cytological abnormalities were more common among SLE patients than controls, even after adjusting for HPV status.

Klumb et al. [21] looked into HPV prevalence among SLE patients and reported that these patients have a high prevalence of HPV infection. Similarly, in a large multicenter croos-sectional study conducted in Korea, SLE patients were shown to have a greater prevalence of Hr-HPV infection and of abnormal cervical cytology compared with healthy controls (24.6% vs 7.9%, and 16.4% vs 2.8%, respectively) [22]. In a systematic literature review evaluating autoimmune patients, it was emphasized that the Hr-HPV prevalence was higher in SLE patients compared to the control groups, while it was comparable in studies on RA and SSc patients [9]. In an another study conducted with Mexican SLE and RA patients, the prevalence of cervical HPV infection was found to be higher compared to the control group [23]. In a population based study conducted in Sweden, the relationship between RA and cervical cancer was investigated and it was suggested that cervical dysplasia increased in RA patients compared to the general population, and invasive cervical cancer increased in RA patients treated with TNF [24]. On the other hand, some studies have shown that cervical dysplasia is not increased in RA patients [25].

In our study, we found that the overall prevalence of Hr-HPV infection was 7.7% among Turkish rheumatologic patients subjected to routine gynecologic examination. In autoimmune and non-autoimmune subgroups, it was 7.3% and 8.0%, respectively. Contrary to the studies in the literature, HPV prevalence was found to be slightly lower in Turkish rheumatology patients compared to the healthy control group without a statistical difference.

As with HPV, statistical difference was not found in terms of cervical cytological abnormalities between rheumatology patients and healthy controls. The overall prevalence of cytological abnormality was 4.4% in RDs and 6.6% in HCs.

Limitations

As in others, this study had some limitations. Patients were questioned by phone about clinical features that may affect the prevalence of HPV, birth control methods or the number of lifetime sexual partners. However, due to Turkey's socio-cultural characteristics, either no answers were received or reliable answers could not be obtained by phone. This was one of the important limitations of this study. The immune status of rheumatology patients is directly related to the immunosuppressive drugs used as well as the disease itself. In this study, drug use was not evaluated, and this was another important limitation.

Evaluation of both autoimmune and non-autoimmune groups by dividing rheumatology patients in a pool is the main strength of the study. Most of the studies in the literature were performed only with autoimmune disease patients.

Conclusion

It was determined that chronic systemic inflammation, resulting from the pathogenesis of rheumatological diseases, and immunosuppressive agents used in the treatment of rheumatological diseases, did not increase the prevalence of Hr-HPV infection and cervical cytological abnormalities. Therefore, sexually active female patients diagnosed with RDs should be screened similar to the normal healthy population in terms of Hr-HPV infection and cervical cytological abnormalities, even if they are receiving immunosuppressive therapy.

References

1. Muñoz N, Bosch FX, de Sanjosé S, Shah KV. The role of HPV in the etiology of cervical cancer. Mutat Res Mol Mech Mutagen. 1994;305:293–301.
2. Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer. 2003;88:63–73.
3. Sawaya GF, Smith-McCune K, Kuppermann M. Cervical Cancer Screening: More Choices in 2019. JAMA. 2019;321:2018–9.
4. Stoler MH. New Bethesda Terminology and Evidence-Based Management Guidelines for Cervical Cytology Findings. JAMA. 2002;287:2140.
5. Castle PE, Sideri M, Jeronimo J, Solomon D, Schiffman M. Risk assessment to guide the prevention of cervical cancer. Am J Obstet Gynecol. 2007;197:356.e1-6.
6. Tchetina E, Markova G. The clinical utility of gene expression examination in rheumatology. Mediterr J Rheumatol. 2017;28:116–26.
7. Baillet A, Gossec L, Carmona L, Wit M de, van Eijk-Hustings Y, Bertheussen H, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis. 2016;75:965–73.
8. Kim SC, Feldman S, Moscicki A-B. Risk of human papillomavirus infection in women with rheumatic disease: cervical cancer screening and prevention. Rheumatology. 2018;57 suppl_5:v26–33.
9. Furer V, Rondaan C, Heijstek M, van Assen S, Bijl M, Agmon-Levin N, et al. Incidence and prevalence of vaccine preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD): a systemic literature review informing the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD. RMD Open. 2019;5:e001041.
10. Nath R, Mant C, Luxton J, Hughes G, Raju KS, Shepherd P, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis Rheum. 2007;57:619–25.
11. Nayar R, Wilbur DC. The Pap Test and Bethesda 2014. Acta Cytol. 2015;59:121–32.
12. Cook DA, Mei W, Smith LW, van Niekerk DJ, Ceballos K, Franco EL, et al. Comparison of the Roche cobas® 4800 and Digene Hybrid Capture® 2 HPV tests for primary cervical cancer screening in the HPV FOCAL trial. BMC Cancer. 2015;15:968.
13. Salazar KL, Duhon DJ, Olsen R, Thrall M. A review of the FDA-approved molecular testing platforms for human papillomavirus. J Am Soc Cytopathol. 2019;8:284–92.
14. Jamdar F, Farzaneh F, Navidpour F, Younesi S, Balvayeh P, Hosseini M, et al. Prevalence of human papillomavirus infection among Iranian women using COBAS HPV DNA testing. Infect Agent Cancer. 2018;13:6.
15. Gultekin M, Kucukyildiz I, Karaca MZ, Dundar S, Boztas G, Turan SH, et al. Trends of Gynecological Cancers in Turkey: Toward Europe or Asia? Int J Gynecol Cancer. 2017;27:1525–33.
16. Demir ET, Ceyhan M, Simsek M, Gunduz T, Arlier S, Aytac R, et al. The prevalence of different HPV types in Turkish women with a normal Pap smear. J Med Virol. 2012;84:1242–7.
17. Yuce K, Pinar A, Salman MC, Alp A, Sayal B, Dogan S, et al. Detection and genotyping of cervical HPV with simultaneous cervical cytology in Turkish women: a hospital-based study. Arch Gynecol Obstet. 2012;286:203–8.
18. Dursun P, Senger SS, Arslan H, Kuşçu E, Ayhan A. Human papillomavirus (HPV) prevalence and types among Turkish women at a gynecology outpatient unit. BMC Infect Dis. 2009;9:191.
19. Al-Sherbeni HH, Fahmy AM, Sherif N. Predisposition to Cervical Atypia in Systemic Lupus Erythematosus: A Clinical and Cytopathological Study. Autoimmune Dis. 2015;2015:1–5.
20. Tam L-S, Chan AYK, Chan PKS, Chang AR, Li EK. Increased prevalence of squamous intraepithelial lesions in systemic lupus erythematosus: Association with human papillomavirus infection. Arthritis Rheum. 2004;50:3619–25.
21. Klumb E, Pinto A, Jesus G, Araujo M, Jascone L, Gayer C, et al. Are women with lupus at higher risk of HPV infection? Lupus. 2010;19:1485–91.
22. Lee Y-H, Choe J-Y, Park S-H, Park Y-W, Lee S-S, Kang Y-M, et al. Prevalence of Human Papilloma Virus Infections and Cervical Cytological Abnormalities among Korean Women with Systemic Lupus Erythematosus. J Korean Med Sci. 2010;25:1431.
23. Rojo-Contreras W, Olivas-Flores E, Gamez-Nava J, Montoya-Fuentes H, Trujillo-Hernandez B, Trujillo X, et al. Cervical human papillomavirus infection in Mexican women with systemic lupus erythematosus or rheumatoid arthritis. Lupus. 2012;21:365–72.
24. Wadström H, Frisell T, Sparén P, Askling J, ARTIS study group. Do RA or TNF inhibitors increase the risk of cervical neoplasia or of recurrence of previous neoplasia? A nationwide study from Sweden. Ann Rheum Dis. 2016;75:1272–8.
25. Chadwick L, Kearsley-Fleet L, Brown N, BSRBR-RA Control Centre Consortium, BSRBR-RA Contributors Group, Watson KD, et al. Cervical screening uptake and rates of cervical dysplasia in the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology. 2019;kez277.

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