



## CASE STUDY

### ADVANCED CERVICAL CANCER AFTER NORMAL SCREENING BY PAPANICOLAOU SMEAR TEST; PRESENTATION OF THREE CASES

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#### ABSTRACT

Due to the growing prevalence of cervical cancer and turning it into a national health problem in developing countries, the best screening method is always considered. Herein we are going to report three cases of false negative tests of pap smear test, which is the main screening method in Iran. Our patients were 31,35 and 37 years old respectively, who did not have any evidences in favor of precancerous cervical lesions in regular screening by pap smear test but eventually were diagnosed as locally invasive squamous cell carcinoma of the cervix. Two of them had out-of-wedlock sex, and one, was heavy smoker on their past history. Although pap test has a good accuracy for differentiation between normal and abnormal cervical cells, but in false negative cases, because of delay in early diagnosis can leads to advanced stages of cervical cancer and poor outcomes. Therefore, it may be better to use complementary methods for screening in high-risk individuals.

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## INTRODUCTION

The incidence of cervical cancer varies from place to place, and against to developed countries, its prevalence has declined due to the widespread coverage of Human Papilloma Virus (HPV) vaccination, in underdeveloped countries, it has a higher incidence and is sometimes a serious health problem (Ferlay *et al.*, 2012). leading cause of death in the world is 27500 in year of which 80% is related to developing countries (de Freitas *et al.*, 2014). The cause of cervical cancer control in advanced societies, other than exact screening program, is related to the broad coverage of HPV vaccination which are not common in Iran. Types of screening methods for cervical cancer have been studied, visual inspection (VI), pap smear test, HPV DNA test for example raised. The goal of all these tests is to actually reduce mortality through early detection and early stage disease diagnosis (Sankaranarayanan *et al.*, 2001). Each of these methods has false negative, leads to delay in diagnosis, advanced stages and poor outcome as a result. This is a dilemma not only medical but legal issue (Maryam Ameri

*et al.*, 2015). In this article, we describe three patients of a locally advanced cervical cancer, despite of having previous normal cytological tests during the scheduled screening program. They were our patients in Gynecology Oncology Department of Imam Khomeini Hospital of Tehran University of Medical Sciences, Tehran, Iran.

### Case presentation

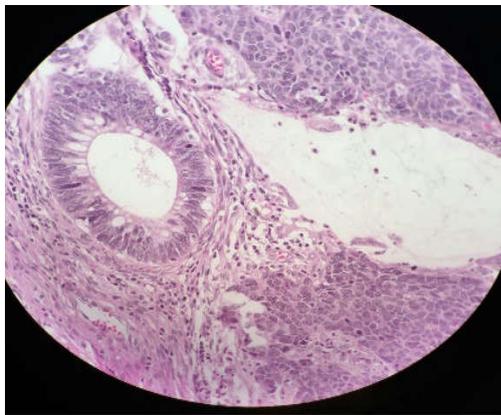
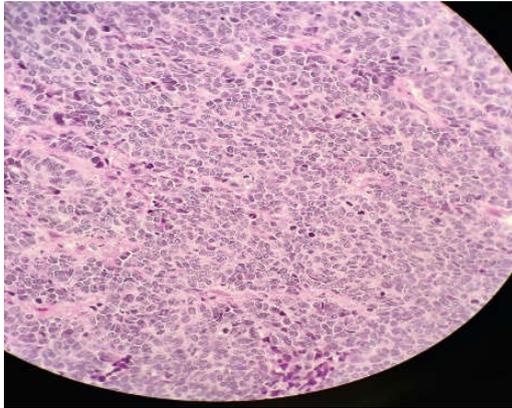
#### Case 1

A 31 years old woman, gravida 1, who was married 10 years ago. Her past medical history was unremarkable, but she was heavy smoker. She was performed 3 pap smear tests during 10 years and all of them were normal without any evidences in favor of pre-invasive cells. Her last normal test was eight months before referring due to vaginal malodor discharge. On exact physical examination, there was a lesion with a diameter of not more than 3 centimeters covered the entire cervical surface, left parametrium was firm and fixed. Microscopic evaluation revealed poorly differentiated squamous cell carcinoma of the cervix. Comprehensive imaging study confirmed cervical cancer stage 2 b. So chemo-radiation was

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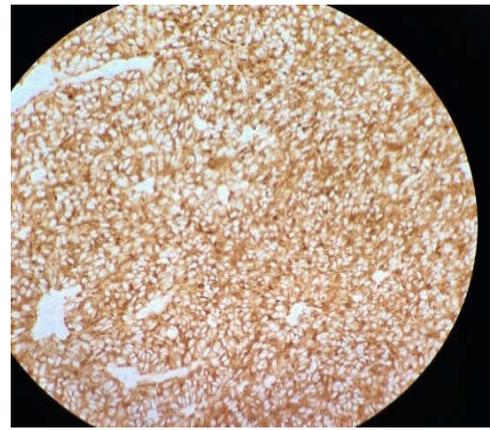
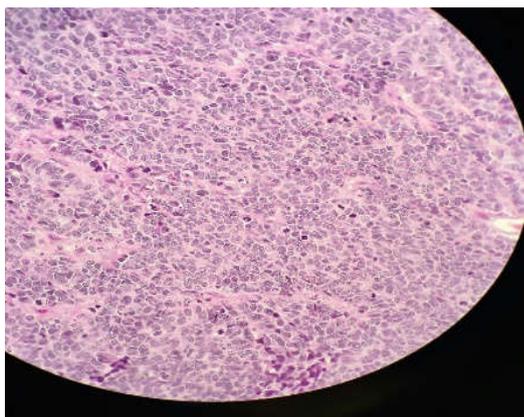
considered and she is free of sign during two years of follow up. Based on her history, second opinion of her last smear was done by an expert pathologist, nevertheless there is no premalignant cell Figure 1,2.



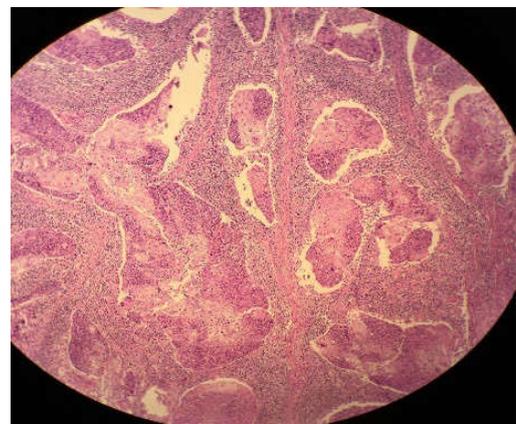
**Figure 1, 2.** These microscopic examinations show poorly differentiated squamous cell carcinoma of the cervical mass

### Case 2

A 35 years old woman gravida 2, with 4 previous normal pap tests within 9 years, referred us with abnormal uterine bleeding. The last normal pap test was about 9 months ago. She had two caesarian deliveries of two her marriages and she was single at the time of the visit. On vaginal inspection, there was a large endophytic mass, about five centimeters in size, which was diagnosed as a well differentiated squamous cell carcinoma of the cervix during histopathological evaluation. Due to the large size of the mass, three courses of neo-adjuvant chemotherapy and subsequent hysterectomy was planned. Second opinion of histopathology confirmed the false negative of pap smear test as well. She is free of recurrence to now. Figure 3,4



**Figure 3, 4.** These microscopic examinations and immunohistochemistry show poorly differentiated squamous cell carcinoma of the cervical mass



**Figure 5.** The microscopic examination is showing a well differentiated squamous cell carcinoma of the cervix

### Case 3

A 37 years old woman with two cesarean deliveries with two normal pap smear test during five years of screening, referred us with post coital bleeding and persistent vaginal discharge without response to conventional treatment. There is a lesion with three centimeter in size on posterior and lateral lip of the cervix, extended to the upper vaginal wall. Histopathological diagnosis was poorly differentiated squamous cell carcinoma of the cervix. After imaging studies and patient presentation in our joint committee in Gynecology Oncology Department of Imam Khomeini Hospital of Tehran University of Medical Sciences, Tehran, Iran, radical hysterectomy type III was planned. because of the depth of invasion was reported in the permanent specimen, chemo- radiation was done. Second opinion of last pap test did not reveal abnormal cells. unfortunately, she experienced recurrence of cervical cancer and died due to renal insufficiency and uremia. Figure 5 At Imam Khomeini Hospital as a routine, at the onset of admission, patients fill the consent form in which the patient was allowed to use her file for future research.

### DISCUSSION

In developing countries, cervical cancer, which can be prevented, is one of the most common cause of death due to gynecologic cancer. Two major ways to reduce mortality are : Vast coverage of HPV vaccine in society and comprehensive planned screening of cervical cancer (Institute for Health

Metrics and Evaluation, 2011). HPV virus is the main cause of cervical intraepithelial neoplasia as such, the high-risk types of the virus contribute to cancer progression. In most women, HPV disappears within 9-15 months, but in some cases, it persists and progresses to pre-neoplastic and neoplastic lesions (Ho *et al.*, 1998). Factors such as immune deficiency and cigarette smoking seem to play a role in creating the ground for viral persistence (Bernard *et al.*, 2013). Despite the repeated recommendations of Gynecology Oncologists in Iran, still the HPV vaccine has not been included in the health and prevention protocol of the country. Therefore, women follow a screening program that performs pap smear test every 3 to 5 years. Numerous studies have reported sensitivity 30% to 87% and specificity 86% to 100% for conventional pap test (Nanda *et al.*, 2000), for example, a recent study in Iran showed sensitivity and specificity 18.2% and 98% respectively for detecting abnormal cells in immunosuppressive patients. In this study colposcopy had higher sensitivity about 66.7% (Mojgan Karimi-Zarchi *et al.*, 2015). Another study in India compared three methods of screening in large population, and the results were as follows: sensitivity and specificity 70% and 84.32% respectively for VI, sensitivity and specificity 62% and 93% respectively for conventional pap smear test, sensitivity and specificity 77.8% and 91% respectively for HPV DNA test. The study suggested that despite of the lesser sensitivity of the VI method, due to the cheaper and more feasibility, it can be preferred in poor societies (Saurabh Bobdey *et al.*, 2016). Medicinal, microbial and hormonal effects can lead to cytogenetic changes and false negative results in pap smear tests (Woodruff *et al.*, 1993). In two studies, the false negative results in pap smear test are often related to immunosuppressed patients and so they recommended colposcopy as first method of screening in this group (Cordiner *et al.*, 1980; Branca *et al.*, 2001). In another study Neisseria gonorrhoea and Trichomonas vaginitis were related to false negative of pap smear result, so it is recommended to use other screening method such as VI, HPV DNA test and even colposcopy in poorer societies with higher incidence rate of sexual transmitted disease (Ross *et al.*, 2015). Some parameters have been proposed to reduce false negatives, which included: Nuclear area (NE), Cytoplasmic area (CA), and nucleus- to- cytoplasmic area ratio (NA/CA) which were shown to increase the diagnostic accuracy of pap smear results (Punit *et al.*, 2011).

We discussed about three patients with normal previous pap smear results, with locally invasive cervical cancer, in all cases, it lasted less than a year since the last time it was screened. All three of them behaved in a high-risk group such as multi partner and heavy smoker. Cancer was reported poorly differentiated in two cases and well differentiated in one, as well one of them died due to recurrence of disease. According to the fact that the result of the false negative result of pap test leads to a delayed cure, this issue is legally also. Therefore, it is necessary to compare different screening methods in our country, and giving that HPV virus is the main cause of cervical cancer, it seems, the vast coverage of HPV vaccination by the Ministry of Health officials is the best option to reduce the mortality rate of this common cancer.

## Conclusion

Although pap smear test is an effective screening method to detect pre-malignant cells, and accepted in the screening protocol, but it is necessary to pay a lot of attention to how to take samples, because false negative cases can postpone timely

treatment result in poor outcomes. It is also important to explain to the patient about some conditions of rapid growth and aggressive behavior of the tumor. In the end, it seems that in a high-risk woman, it is better to use a complementary method such as HPV DNA test, VI and colposcopy to reduce mortality rate of cervical cancer.

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## Conflict of interest

All authors have no conflict of interest to declare.

## REFERENCES

- Bernard E, Pons-Salort M, Favre M, Heard I, Delarocque-Astagneau E, Guillemot D, *et al.* 2013. Comparing human papillomavirus prevalences in women with normal cytology or invasive cervical cancer to rank genotypes according to their oncogenic potential: a meta-analysis of observational studies. *BMC Infectious Diseases*, 13(1):1–11. doi: 10.1186/1471-2334-13-373. PMID: PMC3751808
- Branca M, Rossi E, Alderisio M, Migliore G, Morosini PL, Vecchione A, *et al.* 2001. Performance of cytology and colposcopy in diagnosis of cervical intraepithelial neoplasia (CIN) in HIV-positive and HIV-negative women. *Cytopathology*, 12(2):84–93. doi: 10.1046/j.1365-2303.2001.00299.x. PMID: 11284952
- Cordiner J, Sharp F, Briggs J. 1980. Cervical intraepithelial neoplasia in immunosuppressed women after renal transplantation. *Scottish Medical Journal*, 25(4):275–7.
- de Freitas AC, Coimbra EC, Leitão MdCG. 2014. Molecular targets of HPV oncoproteins: Potential biomarkers for cervical carcinogenesis. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, 1845(2):91–103. doi: 10.1016/j.bbcan.2013.12.004. PMID: 24388872
- Ferlay J, Soerjomataram I, Ervik M, Forman D, Bray F, Dixit R, *et al.* 2012. GLOBOCAN 2012, Cancer Incidence and Mortality Worldwide in 2012. Lyon, France: *International Agency for Research on Cancer*, [Last accessed on 2015 Dec 03]. Available from: <http://www.globocan.iarc.fr>
- Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. 1998. Natural history of cervicovaginal papillomavirus infection in young women. *The New England Journal of Medicine*, 338(7):423–8. doi: 10.1056/NEJM199802123380703.
- Institute for Health Metrics and Evaluation. The Challenge Ahead: Progress in Breast and Cervical Cancer. Institute of Health Metrics and Evaluation. 2011. [Last accessed on 2016 Jan 21]. Available from: <http://www.healthmetricsandevaluation.org/publications/policyreport/challenge-ahead-progress-and-setbacksbreastand-cervical-cancer>.
- Maryam Ameri, Azadeh Memarian, Nadereh Behtash and Mojgan Karimi Zarchi, 2015. The importance of re-examination with deep biopsies in diagnosing cervical malignancies despite multiple negative pathology reports: A case report *Int J Surg Case Rep.*, 14: 48–49. doi:10.1016/j.ijscr.2015.07.010 PMID: PMC4573412
- Mojgan Karimi-zarchi, Leila Zanbagh, Alireza Shafii, Shokouh Taghipour-Zahir, Soraya Teimoori and Pouria Yazdian-Anari, 2015. *Electron Physician*. Comparison of Pap Smear and Colposcopy in Screening for Cervical

- Cancer in Patients with Secondary Immunodeficiency, 7(7): 1542–1548. doi:10.19082/1542 PMID: PMC4700903
- Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD. et al. 2000. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Annals of Internal Medicine*, 132(10):810–9. doi: 10.1056/NEJM199802123380703. PMID:10819705
- Punit VP, Sheela K, Veerendra K, Vidya GD. 2011. Quantitative Cytomorphometric Analysis of Exfoliated Normal Gingival Cells. *J Cytol.*, 28:66–72 PMID: PMC3111711 10.4103/0970-9371.80745
- Ross A. Miller, Lindsay L. Waters, Dina R. Mody and Kimberlee C. Tams, 2015. Squamous Cell Carcinoma of the Cervix: A Cytology-Histology-Human Papillomavirus Correlation in Clinical Practice. *Archives of Pathology & Laboratory Medicine*, Vol. 139, No. 6, pp. 776-781.
- Sankaranarayanan R, Budukh AM, Rajkumar R. 2001. Effective screening programmes for cervical cancer in low- and middle-income developing countries. *Bull World Health Organ.*, 79:954–62. PMID:11693978
- Saurabh Bobdey, Jignasa Sathwara, Aanchal Jain and Ganesh Balasubramaniam, 2016. Burden of cervical cancer and role of screening in India. *Indian J Med Paediatr Oncol.*, 37(4): 278–285 doi: 10.4103/0971-5851.195751 PMID: PMC5234166
- Woodruff JD, Angtuaco TL, Parmley JH, Kurman R. 1993. Atlas of gynecologic Pathology. 2 edition. New York: Raven Press; pp. 1–2.

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