Significant Progression of Uterine Cervical Epithelial Lesion Accompanied by Marked Increase in 3q26 Gene Amplification

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Questions
1. What are some of the essential steps in the oncogenesis of cervical cancer?
2. Why is the 3q26 chromosome region important in the development of cervical cancer?
3. What is 1 of the major problems with the current commonly used tests in cervical cancer screening?
4. How does the oncoFISH cervical test contribute to cervical cancer screening?

Possible Answers
1. Since the 1980s, efforts to understand the oncogenesis of cancer of the cervix have focused largely on the role of certain high-risk human papillomaviruses (HPV). High-risk HPV infections are very common, yet most of these infections do not result in identifiable cytological changes on cervical smears. The high incidence of HPV infections and the low prevalence of high-grade cervical lesions imply that other host cofactors play an important role in the neoplastic process.1,5 Thus, although regarded as necessary, HPV infection by itself is not considered sufficient for the development of cervical cancer; other host changes are now believed essential for the completion of the malignant process.6

2. A major field of research in recent years has focused on identifying molecular markers able to distinguish the low-grade preneoplastic lesions with an indolent course from those with potentially aggressive behaviors. Studies in the molecular cytogenetics of cervical cancer have identified a variety of chromosomal aberrations in cervical cancer and its precursor lesions, the most consistent modifications being detected in the long arm of chromosome 3, where the 3q26 region harbors the human telomerase gene (hTERC) involved in telomere maintenance. Overexpression of this gene has been implicated in tumorigenesis. Additionally, other genes residing

Clinical History
Patient: A 35-year-old Caucasian female
Chief Complaint: Abnormal cervical smear
History of Present Illness and Principal Laboratory Findings: A ThinPrep Pap Test reported atypical squamous cells of uncertain significance in November 2008. The patient tested positive for human papillomavirus type 52 (HPV-52) by polymerase chain reaction (PCR) followed by reverse dot blot. No lesions were identified on colposcopy. An automated fluorescence in situ hybridization (FISH) assay for detection of 3q gain in cervical cells (oncoFISH cervical test, Ikonisys Clinical Laboratory, New Haven, CT) was positive, showing 3 nuclei with at least 5 copies of 3q26 (Image 1). A return visit within 6 months was scheduled, but the patient did not return until 1 year later. A conventional pap smear at that time was interpreted as showing “atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (atypical squamous cells) (HSIL [ASC-H]).” Human papillomavirus type 52 positivity persisted. A repeat oncoFISH cervical test was strongly positive, showing 264 nuclei with at least 5 copies of 3q26 gain (Image 1). Subsequent colposcopy revealed an acetowhite area, of which biopsy showed areas of cervical intraepithelial neoplasia (CIN2-CIN3) with extension into endocervical crypts. She underwent loop electrosurgical excision procedure (LEEP) conization, and histological examination confirmed the biopsy results. The surgical margins of resection were free of the lesion (Image 2).

Past Medical History: Oral contraceptive use, smoking, no abnormal bleeding, no previous gynecological operations.

Keywords: AP Gynecological, cytology, molecular diagnostics, cervical cancer

Abbreviations
PCR, polymerase chain reaction; FISH, fluorescence in situ hybridization; HSIL (ASC-H), high-grade squamous intraepithelial lesion (atypical squamous cells); HPV-52, human papillomavirus type 52; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; HPV, human papillomaviruses; hTERC, human telomerase gene; LSIL, low-grade squamous intraepithelial lesions

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in the 3q26 region such as PIK3CA, which encodes a catalytic subunit of phosphatidylinositol 3-kinase and is associated with a number of cancer-related functions including apoptosis and cellular growth, have the potential of acting as cervical oncogenes. Furthermore, studies have demonstrated that gene amplifications in the 3q26 region are temporally associated with the integration of HPV DNA into the host genome, which constitutes a crucial step in the over production of E6 and E7 oncoproteins that play an important role in the development of cervical cancer.7,8 Additional research has demonstrated a correlation between the gain of 3q26 copy number and the severity and stage of cervical disease progression.7,9,10

3. A major problem of the cervical screening program is the inability of current, commonly used screening tests (ie, cytology, high-risk HPV panels, and HPV genotyping) to distinguish which low-grade lesions of the cervix are destined to either regress or progress to high-grade lesions or malignancies.6 Because of the obvious benefits of being able to identify such lesions, researchers have expended considerable effort to discover molecular markers that would enhance the efficiency of the screening process.11

4. Studies have demonstrated a correlation between the gain in 3q26 copy number and the severity and stage of cervical disease progression.7,9,10 A recent study has examined the potential of using a measure of 3q26 gain as a predictor of regression, persistence, or progression of low-grade squamous intraepithelial lesions (LSIL) of the cervix.12 The case described in this report documents a marked progression in both the severity and extent of this patient’s lesion from atypical squamous cells on cytology to biopsy established CIN2-CIN3 over the span of 1 year. The initial gain of at least 5 copies of 3q26 in only 3 nuclei in this patient’s first cervical smear may be an indication of the significance and sensitivity of this degree of gain, even in a small number of cells at a low level of disease, and may suggest the potential of predicting the progression of the lesion. The subsequent gain of at least 5 copies of 3q26 1 year later in the very large number of 264 nuclei may reflect both the severity and extent of disease progression.
Nevertheless, since it is not possible to exclude the possibility that a high-grade CIN already existed at the time of the initial cytology, the presence of the 3q26 gain, even in a small number of cells, may also serve as an indicator of the possible presence of a high-grade lesion in those cervical specimens in which a definitive cytological diagnosis is not or cannot be made. This case report supports the findings of other investigators on the potential utility of using 3q26 gain in predicting, at an early stage, the progression or non-progression of low-grade preneoplastic lesions of the cervix.12


