Atypical Glandular Cells of Undetermined Significance and Adenocarcinoma In Situ: Summoning Colposcopic Expertise?

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In comparison with cervical squamous neoplasia, glandular cell neoplasia is uncommon. The evaluation of a patient with atypical glandular cells of undetermined significance is challenging because subtle colposcopic signs are frequently inaccessible to view and cytologic interpretations are extremely challenging for many cytopathologists.

KEY WORDS. Vaginal smears; adenocarcinoma; colposcopy; cervical intraepithelial neoplasia. *(J Fam Pract 1996; 43:181-187)*

Compared with cervical squamous cell neoplasia, glandular cell neoplasia is uncommon.[1] Several studies, however, have indicated an increasing incidence of cervical adenocarcinoma in situ (AIS) and adenocarcinoma in women.[2-4] The apparent increased incidence of disease may be due in part to increased detection provided by improved cytologic sampling of the endocervical canal. The natural history of cervical glandular neoplasia is, at present, poorly understood, but human papillomavirus (HPV) likely plays a role.[5] Although less severe glandular neoplasias do not have as clear a progressive potential as that encountered with squamous neoplasia, AIS also appears to be a precursor of adenocarcinoma.[1]

The early detection and diagnosis of AIS and adenocarcinoma of the cervix are problematic and extremely challenging.[6] Cytologic sampling can be hindered if glandular neoplasia occupies only the deep recesses of endocervical clefts, if it is covered by metaplastic epithelium, or if it is located within the poorly accessed endocervical canal.[7] The cytologic diagnosis of adenocarcinoma in situ, or "atypical endocervical cells, probably neoplastic," is especially difficult for many pathologists.[8,9] The colposcopic evaluation of AIS is hampered by subtle colposcopic signs that are frequently inaccessible to view, diagnostically controversial, and considered by many colposcopists to be nonspecific or otherwise not apparent.[6] Controversy also exists regarding the proper treatment of AIS of the cervix.[10,11]

Because of the insidious nature of the glandular neoplasias, diagnosis, treatment, and posttherapy monitoring demand special attention and expertise. The following report illustrates a case of AIS of the cervix detected in a young woman following a routine Papanicolaou (Pap) smear.

Case Report

A 27-year-old single woman, gravida 0 para 0, presented for a routine physical examination and Pap smear in January 1995. She considered herself to be in good health and had no complaints.

Her gynecologic history noted regular menses with mild dysmenorrhea. She denied a history of abnormal Pap smears or sexually transmitted diseases. Her family history was significant for lung cancer and an aunt who had some type of cervical neoplasia.

Her physical examination was essentially normal, except for a white vaginal discharge and a cervix that bled readily to touch. A Pap smear was

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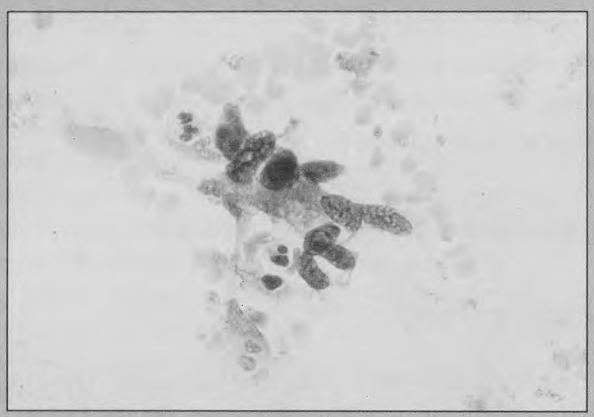
FIGURE 1

Papanicolaou smear showing atypical glandular cells. Elongated cells are arranged radially in a partial "rosette" formation, indicating a columnar or glandular nature. Nuclei are enlarged, and nuclear chromatin is dark and granular (Papanicolaou stain; magnification ×400).



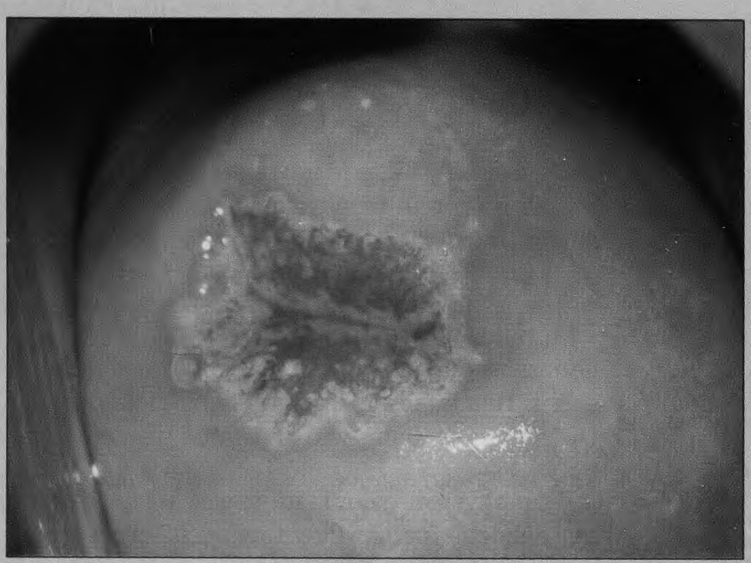
obtained, along with a vaginal saline wet prep, potassium hydroxide, and *Chlamydia trachomatis* test. Except for the Pap smear, these tests were within normal limits. The Pap smear adequacy was satisfactory but limited by inflammation and blood. Atypical glandular cells of undetermined significance (AGUS) were also noted. Based on this result, the patient was scheduled for a repeat Pap smear in 6 months.

A Pap smear was repeated 7 months later. It was reported as satisfactory with atypical endocervical cells (Figure 1). An additional comment by the pathologist suggested that endocervical glandular dysplasia or adenocarcinoma in situ could not be ruled out. Colposcopy was then performed.

The colposcopic examination (Figure 2) was satisfactory, and revealed the late stages of active squamous metaplasia extending within the endocervical canal. There appeared to be two small ill-defined areas of atypical columnar epithelium located at the 7 and 10 o'clock positions on the anterior and posterior lips of the cervix, respectively. The abnormal epithelium was a denser, yellow-acetowhite color compared with the more translucent surrounding metaplastic epithelium. Several "root-like" atypical vessels were also noted. Examination of the distal 1.5 cm of the endocervical canal using an endocervical speculum revealed no significant abnormalities in this area. Two cervical biopsies were taken from the abnormal epithelium, and an endocervical curettage was performed. The colposcopic impression was AIS, rule out occult adenocarcinoma. The patient was also found to have bacterial vaginosis and was treated with metronidazole.

FIGURE 2

Colpophotograph (×15) of cervix demonstrating the complete squamocolumnar junction and an ectropion. Active immature squamous metaplasia is noted. The subtle features of adenocarcinoma in situ cannot be appreciated at this level of magnification.



The histologic specimen of the biopsied tissue revealed cervical AIS (Figure 3). The endocervical curettage revealed fragments of benign endocervical epithelium. The cytologic and histologic interpretations and colposcopic impression correlated within 1 degree of severity. The patient was referred to a gynecologic oncologist for treatment. A cold-knife conization was subsequently performed. The excised cervical specimen revealed adenocarcinoma in situ with no invasive carcinoma. The resected margins were free of neoplasia.

Discussion

The diagnosis of AIS of the cervix is generally fortuitous. The case in this report demonstrates many of the features of

glandular cell neoplasia of the cervix. The woman's age of 27 years, although quite young, is consistent with a reported younger mean age for AIS (39 years) as compared with adenocarcinoma (57 years).[1] The patient was asymptomatic and her disease was detected by routine Pap smear screening, as would be expected.[6,7]. Her case also demonstrates some of the challenges in the diagnosis and management of glandular neoplasia of the cervix.

The difficulty of detecting early glandular neoplasia by cytologic testing is attributed to failure to retrieve cells from typically small lesions located in the endocervical canal and deep gland clefts and to difficulties in microscopic interpretation. The use of cytologic brushes rather than cotton swabs for endocervical sampling minimizes the risk of a false-negative Pap smear. The specificity and sensivity of cervical cytologic testing for glandular neoplasia suffers from the challenge of differentiating many premalignant changes from benign changes at one extreme to malignant conditions at the other.[1,9,12] For glandular cells reflecting nonspecific features that are more severe than reactive or reparative changes but less severe than invasive adenocarcinoma, the Bethesda System of Pap smear classification uses the designation "atypical glandular cells of undetermined significance" (AGUS). In other words, in contrast to ASCUS ("atypical squamous cells of undetermined significance"), AGUS potentially represents the full spectrum of premalignant glandular changes. Our patient's first abnormal Pap smear was reported as AGUS.[8] The AGUS diagnosis should be qualified to indicate origin of atypical cells, either endocervical or endometrial, and the degree of atypia, ie, "favor reactive" or "favor neoplastic."[8] This latter classification would be more suggestive of a possible AIS, which would lead to more intensive evaluation. This was the report of the woman's repeat Pap smear. The differential diagnosis of the AIS Pap smear report is broad, including benign cervical changes, premalignant changes, and possibly invasive cancer of the endocervical canal. The cytologic diagnosis of AIS is easily confused with tubal metaplasia[9] or invasive cancer.[8] Until better cytologic discrimination between AGUS and AIS can be developed, great care should be exercised in the diagnosis and evaluation of these glandular abnormalities of the endocervix. At the present time, differentiation necessitates a histologic specimen.

FIGURE 3

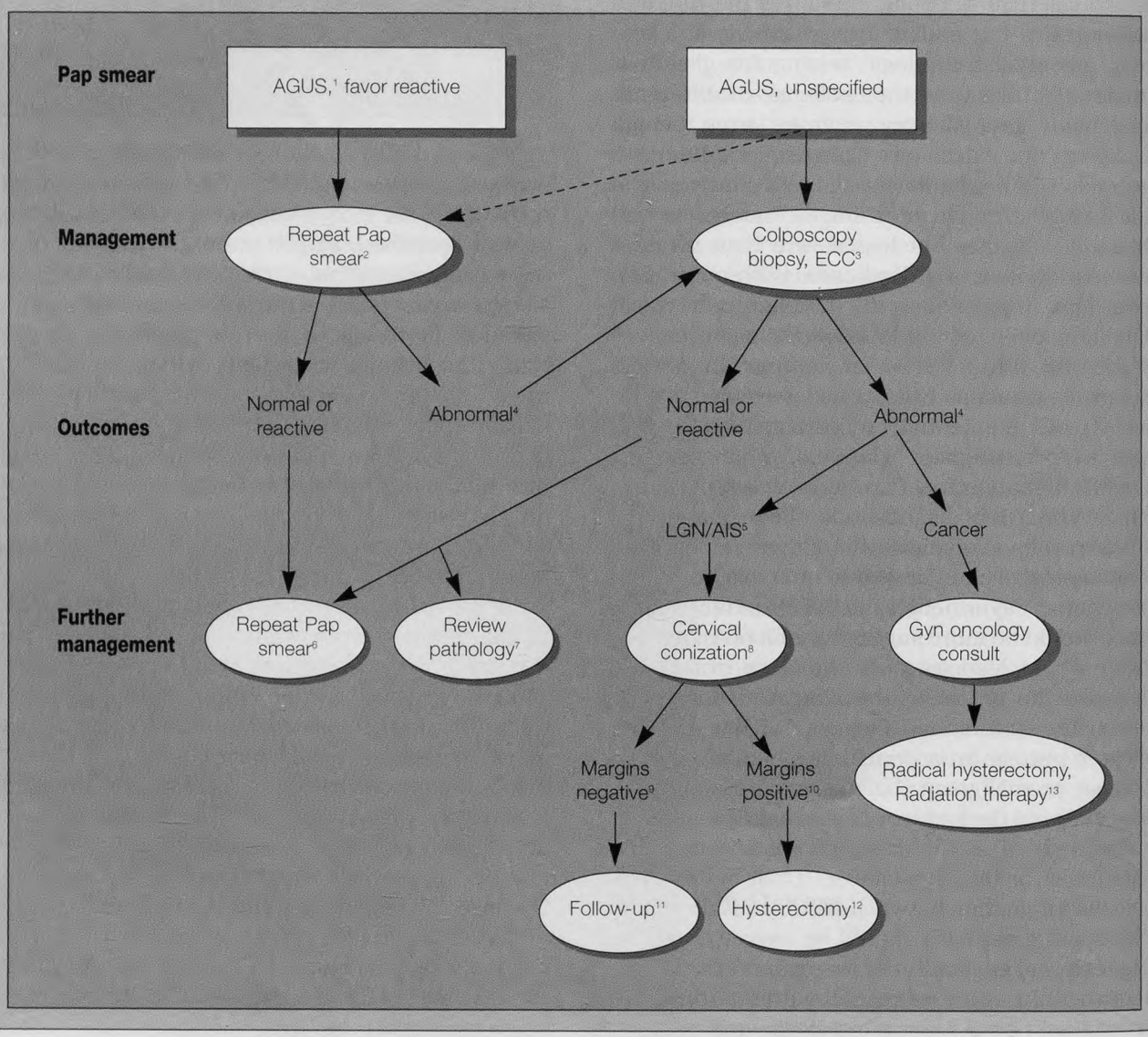
Biopsy showing endocervical adenocarcinoma in situ. Endocervical glands have crowded, elongated, hyperchromatic nuclei in some areas with decreased mucin production (hematoxylin and eosin stain; magnification ×200).

Most physicians believe it is impossible to diagnose AIS colposcopically.[11-13] The colposcopic features of AIS are most often nonspecific and are not as well described, agreed upon, or clinically obvious. Coppelson,[10] however, suggests that AIS lesions have a "stark acetowhiteness of either individual or fused villi in discrete patches of varying size." The lesions are usually within or near the transformation zone and may be surrounded by normal-appearing villi. It is clear that it is extremely difficult, if not impossible, to distinguish immature metaplasia from AIS. In the case presented, the colposcopically directed cervical biopsies were successful in revealing AIS. The colposcopic impression of this abnormal tissue could be uncritically described as "just not looking right"; however, the yellowish acetowhite tint of the epithelium, the small, vaguely atypical blood vessels, and the contrasting density when compared with the surrounding more translucent, thin, immature squamous metaplasia subtly guided the experienced colposcopist to the correct location. Similar findings may be present in atypical squamous metaplasia. It must be emphasized that histologic confirmation by biopsy or conization is essential. Because AIS may be multifocal, small, or secluded in the endocervical canal, cervical conization is generally recommended to confirm the diagnosis, exclude an occult invasive adenocarcinoma, and serve as possible therapy.

FIGURE 4

Suggested evaluation and management of women with an unspecified Papanicolaou (Pap) smear reported as atypical glandular cells of undetermined significance (AGUS), favor reactive or AGUS. Solid arrows indicate preferred pathways and dotted arrow indicates alternative pathway.

AGUS[1] denotes atypical glandular cells of undetermined significance; **Repeat Pap smear**[2] indicates that it may be appropriate to review the cytologic test results before repeating the Pap smear or performing colposcopy; **ECC**[3] denotes endocervical curettage; **Abnormal**[4] refers to glandular neoplasia; **LGN/AIS**[5] denotes low-grade glandular neoplasia or adenocarcinoma in situ. If adenocarcinoma in situ (AIS) is documented by histologic testing, cervical conization is appropriate for young women who have not completed childbearing; otherwise, hysterectomy should be considered; for low-grade glandular neoplasia (LGN), cervical conization is appropriate. **Repeat Pap smear**[6] indicates that Pap smear should be repeated every 4 to 6 months until 3 successive smears are normal. If any repeat Pap smear reveals glandular neoplasia, colposcopy or cervical conization, or both, should be performed. **Review pathology**[7] indicates that if histologic test results are negative and cytologic testing suggests AIS, site undetermined, further evaluation by, for example, hysteroscopy, endometrial biopsy, dilation and curettage, cervical conization, or pelvic ultrasound, should be considered. **Cervical conization**[8] denotes conization 20 to 25 mm deep; **Margins negative**[9] refers to conization margins that are free of neoplasia; **Margins positive**[10] refers to conization margins demonstrating glandular neoplasia; and **Follow-up**[11] refers to follow-up by cytologic testing and colposcopy during the first postoperative year. An exception to **Hysterectomy**[12] is that if the patient is young and the cone is of adequate depth, she may be followed carefully with Pap smear and ECC as an alternative. **Radical hysterectomy, Radiation therapy**[13] indicates that this therapy assumes previous histologic confirmation of adenocarcinoma.



The histologic diagnosis of adenocarcinoma in situ must consider multiple anatomical and architectural patterns and cytologic features.[14] The epithelium is multilayered or pseudostratified in contrast to normal single-layered columnar epithelium.[7] The nuclei are vertically oriented, and there is an increased nuclear-to-cytoplasmic ratio, increased nuclear hyperchromasia, and a variable degree of pleomorphism and mitotic activity.[7] Because of varied distribution of endocervical glands within the stroma, the histologic discrimination of AIS vs adenocarcinoma is extremely challenging.[15]

The differential diagnosis of a Pap smear reported as AGUS is broad and includes benign and neoplastic changes of both squamous cell and glandular cell origin. After careful evaluation, a significant number of women with an AGUS Pap smear report are found to have squamous neoplasia. Furthermore, AGUS is rarely reported by laboratories (<1 % of the cases of abnormal Pap smear) and the majority of AGUS reports are classified as "unspecified" or "favor reactive changes." The additional definition of "favor neoplasia or AIS" is nearly as broad but slants toward the neoplastic spectrum. Clearly, cytologic testing alone is unreliable either to diagnose or to exclude glandular neoplasia. The evaluation of the patient with atypical glandular cells in her Pap smear demands caution and the experience of experts.

One example of AGUS management is shown in Figure 4. The frequency of this finding and its positive predictive value for neoplasia is uncertain. Because of this uncertainty, the spectrum of evaluation ranges from aggressive to conservative. It may be appropriate to repeat a Pap smear for the patient reported to have "AGUS unspecified" or "AGUS favor reactive."[16] This was the management selected for our patient's first Pap smear report. Aggressive evaluation by colposcopy, endocervical curettage, and cervical biopsy may be more apt than cytologic testing alone to detect the rare occult malignancy. Negative findings using either approach, however, do not ensure the absence of glandular neoplasia in the more proximal genital tract, where it would be secluded from sampling or visualization. Other diagnostic options should therefore be considered. For the patient with persistent cytologic atypia, cervical conization or uterine curettage or both may be necessary.

The management of AIS is also controversial (Figure 5).[10] Many argue that the cytologic or histologic diagnosis of AIS demands cervical conization. That one third of patients with glandular neoplasia on Pap smears have invasive cancer strongly supports this approach.[17] This comment, however, represents one investigator's findings and is based on the "microinvasive" classification of many cancers that other pathologists find difficult to diagnose. Colposcopic evaluation may lead to a definitive diagnosis, but until a diagnosis is obtained, a negative colposcopic examination of a woman with AIS requires a cervical conization. Luesley et al[13] demonstrated that colposcopy and biopsy predicted less than one third of women in whom glandular dysplasia was later detected by subsequent cervical conization or hysterectomy. The colposcopic examination, however, may be additionally useful to exclude the presence of coexisting squamous cell neoplasia.[18]

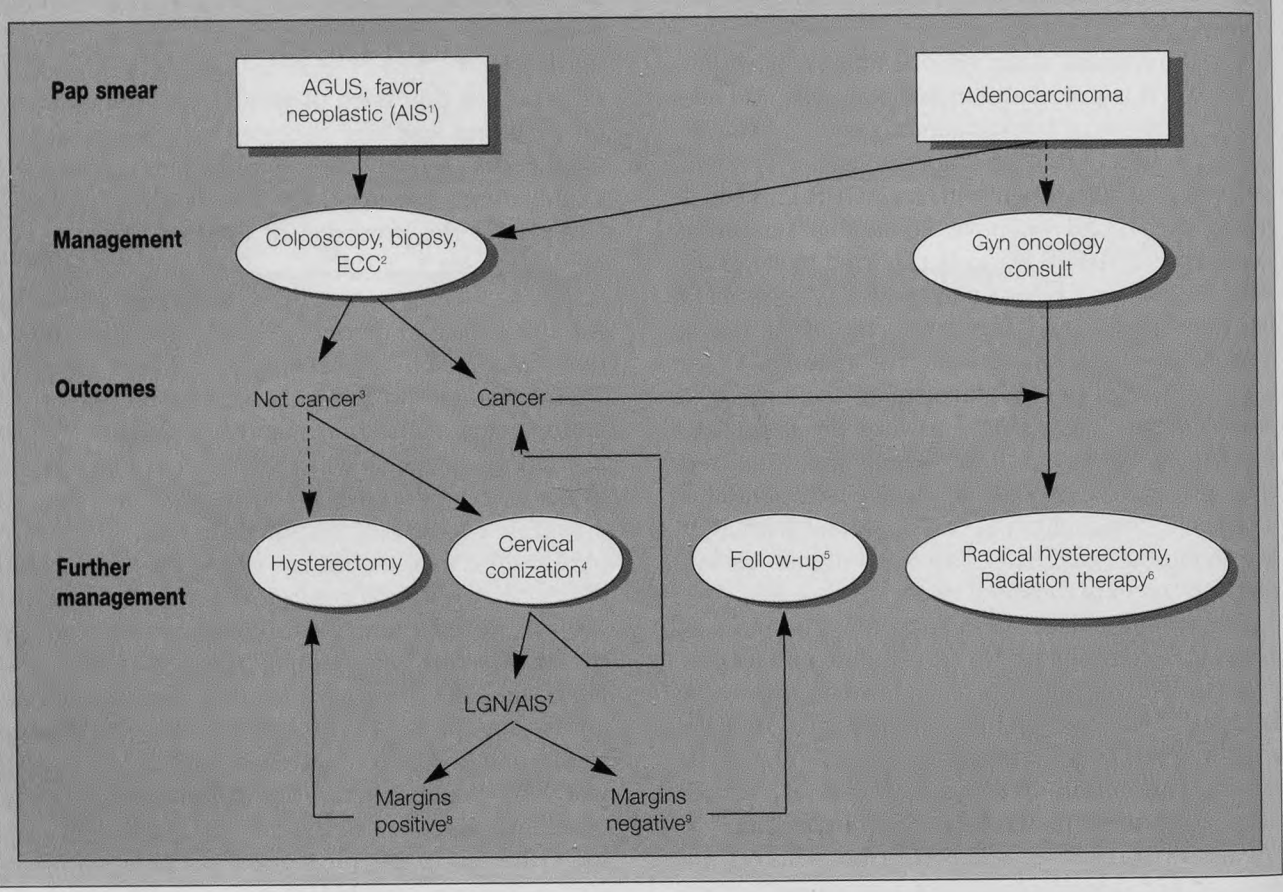
Cervical conization may be used concomitantly for diagnosis and therapy. A cone biopsy should be performed when colposcopy, biopsy, and endocervical curettage do not fully explain the abnormal endocervical cells confirmed by secondary review of the Pap smear or when subsequent Pap smears indicate a continued glandular abnormality. A cylindrical conization 25-mm deep has been shown to be curative for the majority of women.[7] Provided the cervical conization surgical margins are free of disease, women may be followed postoperatively by colposcopy, cervical cytologic testing, and endocervical curettage. A positive conization margin is thought to require hysterectomy. Cullimore et al[19] demonstrated that the majority of women who have positive conization margins do not have residual disease detected at hysterectomy. Nevertheless, some physicians continue to advocate mandatory simple hysterectomy for treatment of AIS.[11] Such an approach is more persuasive if a woman has completed her childbearing or has another indication for hysterectomy. When electing conization instead of hysterectomy, it is extremely important to have a reliable patient who has been informed of the need for posttreatment cytologic and colposcopic follow-up.

What, then, is the role of colposcopy in evaluating women with abnormal glandular cell cytologic test results? As demonstrated in this case, AIS can be presumptively diagnosed, albeit tenuously, by

FIGURE 5

Suggested evaluation and management of women with AGUS, favor neoplastic or adenocarcinoma Pap smear report. Solid arrows indicate preferred pathways, and dotted arrow indicates alternative pathway.

AIS[1]denotes adenocarcinoma in situ; **ECC**[2] denotes endocervical curettage. **Not cancer**[3] indicates that if histologic testing is negative and cytologic testing suggests AIS, site undetermined, further evaluation by, for example, hysteroscopy, endometrial biopsy, dilation and curettage, cervical conization, or pelvic ultrasound should be considered. If AIS is documented by histologic testing, cervical conization is appropriate for young women who have not completed childbearing; otherwise, hysterectomy should be considered; for low-grade glandular neoplasia (LGN), cervical conization is appropriate. **Cervical conization**[4] denotes conization 20- to 25-mm deep; **Follow-up**[5] indicates follow-up by cytologic testing and colposcopy during the first postoperative year; **Radical hysterectomy, Radiation therapy**[6] indicates that this therapy assumes previous histologic confirmation of adenocarcinoma; **LGN/AIS**[7]denotes low-grade glandular neoplasia or adenocarcinoma in situ; **Margins positive**[8] indicates that conization margins demonstrate glandular neoplasia; and **Margins negative**[9] indicates that conization margins are free of neoplasia.



colposcopy and directed cervical biopsy. Somewhat nonspecific colposcopic signs that implied "abnormality" were apparent in this case. Yet, because glandular dysplasia may be located within endocervical clefts or the proximal endocervical canal, a negative colposcopic examination may indicate missed occult disease, and a positive test may underestimate the severity of disease by simultaneously overlooking occult carcinoma. On the contrary, colposcopy should detect flagrant invasive adenocarcinoma, and also allow recognition of coexisting or independent squamous cell neoplasia, estimated to occur in 50% of cases. Still, a histologic biopsy finding positive for squamous cell neoplasia may not explain the origin of a glandular cell cytologic abnormality.

An AGUS cytologic test report demands serious assessment. To improve the diagnosis of glandular neoplasias in the future, further critical appraisal and delineation of specific cytologic criteria for these neoplasias is needed.[20] Clarification of the abnormal colposcopic signs for AIS is necessary

and would benefit the management of early glandular cell neoplasia.

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