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Clinical significance and management of cervical atypical glandular cells of undetermined significance

不明宮頸腺體細胞異常的臨床重要性及處理

Objectives. To assess the clinical significance of a cervical cytological diagnosis of atypical glandular cells of undetermined significance and to formulate the most appropriate management guidelines for patients with such a diagnosis.
Design. Retrospective study.
Setting. Regional hospital, Hong Kong.
Patients. Seventy-two patients with diagnoses of atypical glandular cells of undetermined significance who were managed in a colposcopy clinic between January 1998 and December 1999.
Main outcome measures. Age, cytological diagnoses of atypical glandular cells of undetermined significance and its subtypes, method of evaluation, final diagnosis, and outcome after 2 years.
Results. Atypical glandular cells of undetermined significance were diagnosed in 83 (0.4%) of 21 854 cervical smear samples taken during the 2-year study period. Follow-up data were available from 72 patients, whose mean age was 43 years (range, 22-69 years). Forty-three percent of these patients had significant diseases of the genital tract. Patients with the subtype diagnosis of atypical glandular cells of undetermined significance–favour neoplasia had the worst outcome, with 90% of patients having significant disease, followed by patients with atypical glandular cells of undetermined significance 'not otherwise specified' (43%), and atypical glandular cells of undetermined significance-favour reactive (8%).
Conclusion. Patients with atypical glandular cells of undetermined significance should be investigated early and thoroughly, because many of them will have premalignant or malignant disease.

目的：評估對不明腺體細胞異常作宮頸細胞檢查的臨床重要性，並制訂對此類患者最適當的醫療指引。
設計：回顧研究。
安排：香港一所地區醫院。
患者：在 1998 年 1 月至 1999 年 12 月期間， 72 位被發現宮頸腺體細胞出現異常但性質未定的病人；他們都在門診接受了陰道鏡跟進檢查。
主要結果測量：年齡、對不明宮頸腺體細胞異常及其類型所作的細胞學檢查、評估方法、最後診斷，以及兩年後的結果。
結果：在兩年研究期間， 21 854 個宮頸塗片樣本中，發現 83 個(0.4%)不明腺體細胞異常個案。其中 72 人的跟進資料齊全；她們的平均年齡為 43 歲(範圍， 22-69 歲)，其中43%患有嚴重的生殖道疾病。兩年後的跟進結果顯示，有形成新生物傾向的不明異常腺體細胞患者，其情況最差，有 90% 患上重症；其次為未能分類的不明異常腺體細胞(43%)，及不明異常腺體細胞呈活性反應者(8%)。
結論：腺體細胞異常而其性質不明的患者，應及早接受全面檢查；因她們往往會患上癌變前或惡性病症。

Key words:
Atypical glandular cell of undetermined significance; Vaginal smears

關鍵詞：
不明腺體細胞異常；陰道抹片

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Introduction

Atypical glandular cells of undetermined significance (AGUS) is a cytological diagnosis within the category of glandular cell abnormality in the Bethesda system of reporting cervical cytological diagnoses.[1] A cytological diagnosis of AGUS is

defined as the presence of glandular cells exhibiting changes beyond reactive or reparative changes but lacking unequivocal features of invasive adenocarcinoma. Because it is a diagnosis of exclusion, these changes may represent a florid response to inflammation, a precursor neoplastic lesion, or a non-representative cell sampling of neoplastic tissue. Moreover, there is no consensus on the meaning of AGUS among pathologists, and a report of AGUS often causes confusion and sometimes debate among clinicians, because its clinical significance is not clearly defined and its management is unsure. This study aimed at increasing our understanding of the clinical significance of AGUS among the Chinese population.

Patients and methods

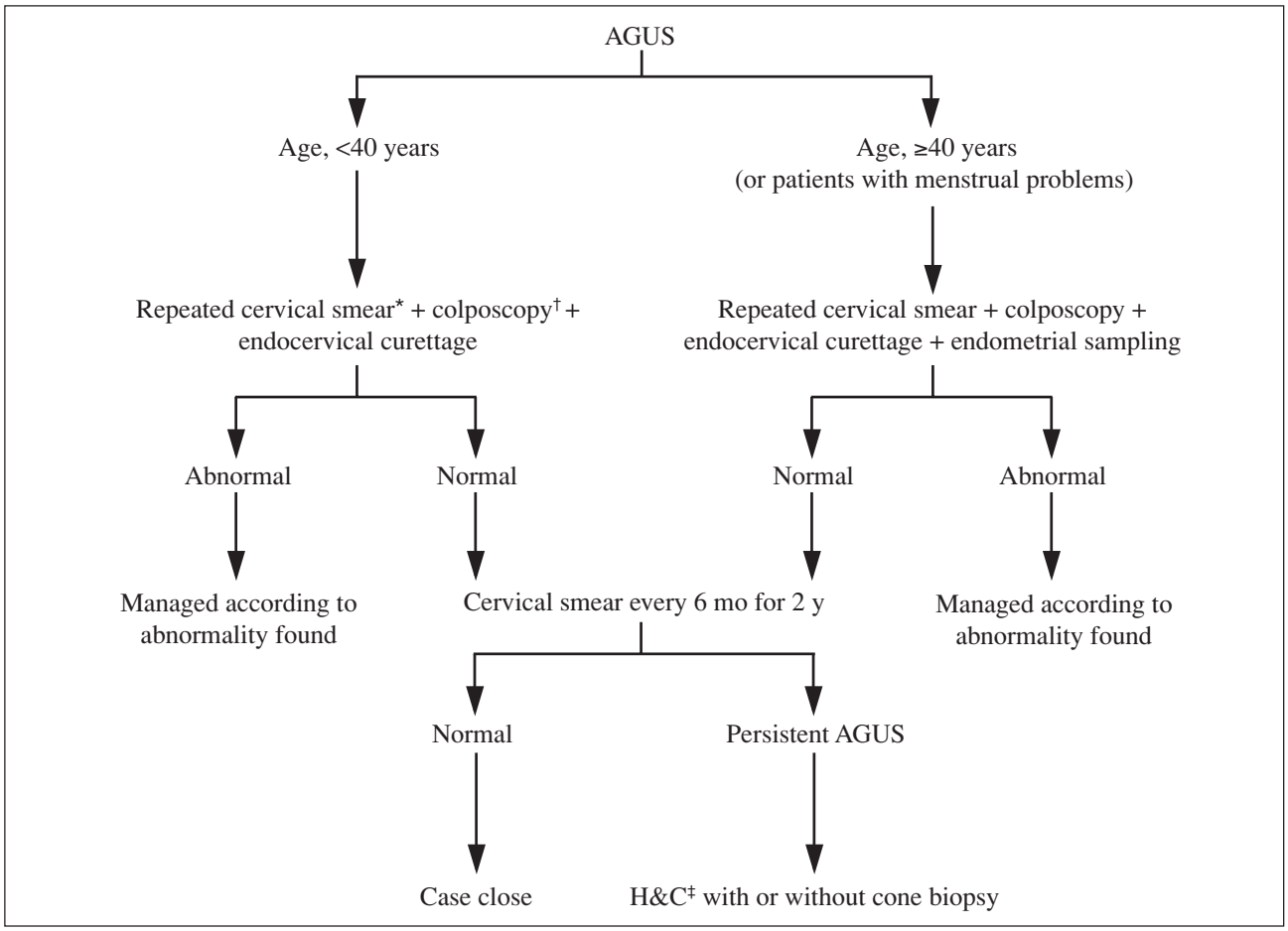
We performed a computer-based search of cytopathology files at the Clinical Pathology Department of the Tuen Mun Hospital to identify patients who received a diagnosis of AGUS between January 1998 and December 1999. The relevant clinical records were retrieved from the record office and the colposcopy clinic for analysis. All the patients with a diagnosis of AGUS were investigated and followed up for at least 2 years in the Colposcopy Clinic at our institution, and were managed according to the algorithm that had been implemented in 1997 in our department (Fig 1). The investigations included cervical smear tests (with an Ayre spatula and an endocervical brush), colposcopy with or without biopsy, endocervical curettage, endometrial sampling with or without hysteroscopy and curettage (H&C), and cone biopsy. Patients who were incompletely investigated or who defaulted follow-up were excluded from the study.

We collected information on patients' age, diagnosis of AGUS and its subtypes, method of evaluation, final diagnosis, and outcome after 2 years. The AGUS and its subtypes were analysed so that we could determine the most appropriate management for this condition. Patients were considered to have a clinically significant lesion if they had premalignant or malignant lesions, which included cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS), endometrial hyperplasia, or carcinoma.

Results

Over the 2-year study period, 21 854 Papanicolaou smear samples were evaluated at our institution, and 83 (0.4%) of

Fig 1. 1997 Guidelines for the management of patients with atypical glandular cells of undetermined significance (AGUS)



* With Ayre spatula and endocervical brush
† Colposcopic examination with or without biopsy
‡ H&C hysteroscopy and uterine curettage

them were interpreted as containing AGUS. Of these 83 cases, 11 were excluded from the study because they were repeated cervical smear samples of the same patients, or the investigations were incomplete, or the patients were not followed up in our Colposcopy Clinic. Of the remaining 72 cases, they were further subclassified into AGUS–not otherwise specified (NOS), AGUS-favour reactive, and AGUS-favour neoplasia. In all, there were 49 cases of AGUS-NOS, 13 AGUS-favour reactive, and 10 AGUS-favour neoplasia. Compared with the 3267 cases of atypical squamous cells of undetermined significance (ASCUS) during the same period, the AGUS rate was very low.

The age of the 72 patients ranged from 22 to 69 years with a mean of 43 years, a finding similar to that in most other studies.[2-5] The final diagnoses of all patients after full investigation and follow-up of 2 years or more are summarised in Table 1. If we count all premalignant and malignant lesions, 31 (43%) patients had significant disease in our series.

When we considered the final diagnoses after subclassification of AGUS (Table 2), cases of AGUS-favour reactive were usually benign in our series of patients. There was only one case of CIN among the 13 cases—that is, only 8% had a clinically significant disease. The opposite held true if the cervical smear revealed AGUS-favour neoplasia: nine (90%) of the 10 patients had significant disease. The cytological finding of AGUS-NOS was the most common (total, n=49) and the incidence of clinically significant disease was intermediate (21 cases; 43%).

Table 3 summarises the detection rate of premalignant and malignant lesions of various investigation methods.

Table 1. Final diagnoses of patients with atypical glandular cells of undetermined significance

Diagnosis*	No. of patients (%)
Normal	9 (12.5)
Human papillomavirus infection of cervical epithelium	30 (41.7)
Cervical intraepithelial neoplasia	14 (19.4)
Adenocarcinoma in situ of the cervix	5 (6.9)
Adenocarcinoma of cervix	6 (8.3)
Chronic endometritis	2 (2.8)
Endometrial hyperplasia	1 (1.4)
Endometrial carcinoma	4 (5.6)
Others	1 (1.4)
Total	72 (100.0)

* Diagnosis only reflected the most significant lesion

Table 2. Correlation of subclassification of cases of atypical glandular cells of undetermined significance (AGUS) with final diagnoses

Histological diagnosis	Cytological diagnosis		
	AGUS-favour reactive process	AGUS-favour neoplastic process	AGUS–not otherwise specified
Normal	3	0	6
Human papillomavirus infection of cervical epithelium	9	1	20
Cervical intraepithelial neoplasia	1	1	12
Adenocarcinoma in situ of the cervix	0	2	3
Adenocarcinoma of cervix	0	4	2
Chronic endometritis	0	0	2
Endometrial hyperplasia	0	0	1
Endometrial carcinoma	0	2	2
Breast carcinoma secondary to uterus	0	0	1
Total	13	10	49

Table 3. Detection rate of premalignant and malignant lesions through each investigation method

Investigation method	Type of lesion		
	Endocervical lesions (n=11) No. of cases (%)	Endometrial lesions (n=6) No. of cases (%)	Squamous cervical lesions (n=14) No. of cases (%)
Repeated cervical smear*	8 (73)	2 (33)	12 (86)
Colposcopy	4 (36)	0	12 (86)
Cervical biopsy	9 (82)	NA‡	14 (100)
Endocervical curettage	6 (55)	0	NA
Cone biopsy†	9 (100)	NA	NA
Endometrial biopsy or hysteroscopy and uterine curettage	0	6 (100)	NA

* Any reports with atypical glandular cells of undetermined significance or significant glandular lesion was counted
† Cone biopsy was done for only nine of the 11 cases of endocervical lesion because two had obvious lesions
‡ NA not applicable

Table 4. Outcome of 15 cases of atypical glandular cells of undetermined significance (AGUS)–specified endometrial cell

Smear test result	Age (years)	Menstrual problem	Final diagnosis
AGUS NOS*	58	None	Atrophic endometritis
AGUS NOS	43	Irregular cycles	HPV† infection
AGUS NOS	39	Irregular cycles	NAD‡
AGUS NOS	40	None	NAD
AGUS NOS	47	None	NAD
AGUS NOS	32	Menorrhagia	CIN§ III + HPV + disordered proliferative endometrium
AGUS NOS	27	None	NAD
AGUS NOS	43	None	NAD
AGUS NOS	46	Menorrhagia	Chronic endometritis
AGUS NOS	42	None	CIN II + HPV
AGUS NOS	47	None	HPV infection
AGUS NOS	32	None	HPV infection
AGUS NOS	65	PMB‖	Endometrial carcinoma
AGUS-favour neoplasia	46	Prolonged menses	Endometrial carcinoma
AGUS-favour neoplasia	44	Menorrhagia	Endometrial carcinoma

* NOS not otherwise specified
† HPV human papillomavirus infection of the cervical epithelium
‡ NAD no abnormality detected
§ CIN cervical intraepithelial neoplasia
‖ PMB postmenopausal bleeding

There were 11 cases of endocervical glandular lesions: six of adenocarcinoma and five of AIS. Cone biopsy yielded the best results, with a 100% detection rate. Only nine of 11 patients had cone biopsies performed, because two had obvious tumour growth over the cervix. Colposcopy alone had a detection rate of only 36%, and this result agrees with experts' opinions that AIS is difficult to diagnose colposcopically.[5,6] However, colposcopy-directed biopsy had a very good detection rate of 82%, which probably reflects the fact that most AIS lesions are closed to the squamous-columnar junction[6] and many endocervical glandular lesions have concurrent squamous lesions.[7,8] In our study, four (36%) patients had CIN lesions at the same time, and cervical biopsy of these lesions led to the discovery of AIS. Furthermore, there were six cases of adenocarcinoma which could be detected easily by colposcopy and biopsy. Endocervical curettage gave a relatively poor result of 55%, which might be unexpected; however, repeated cervical smear testing had a very good detection rate of 73%.

Of the six cases of endometrial lesions, four were adenocarcinoma, one was a secondary tumour from breast, and one was endometrial hyperplasia. Obviously, endometrial biopsy or H&C gave the best detection rate of 100% and repeated cervical smear testing had a rate of only 33%.

For squamous cervical lesions, there were 14 cases all with CIN lesions. Fortunately, there was no squamous cell carcinoma and most of the lesions could be picked up by colposcopy and biopsy. Endocervical curettage appeared unuseful and had a detection rate of 14%.

Of 15 cases of AGUS qualified as endometrial origin, three (20%) cases were endometrial carcinoma (Table 4). All affected patients were perimenopausal, were older than 40 years, and had menstrual problems. There were two (13%) cases of high-grade CIN lesion, although they were qualified as endometrial cell on cytological examination.

Discussion

Since the introduction of the diagnostic category AGUS of the Bethesda system in 1988, the clinician has often faced the dilemma of how patients with this diagnosis should be treated. The histological outcomes of the AGUS are so broad that they include benign and neoplastic changes of both squamous and glandular cells from the cervix, uterus, or even other parts of the body. Slightly more than two fifths of patients had premalignant or malignant disease. This finding agrees with the most recent literature, which reports that 25% to 83% of patients with AGUS have significant disease of the genital tract.[2-7,9-12] Hence, it is incorrect to manage cases of AGUS just like those of AGUS by repeating the cervical smear in a few months' time. The appropriate management should be an early thorough investigation for the cause. Because the AGUS rate of 0.33% was low in our study population, the workload for this problem should not be heavy. In fact, most of the recent reports revealed an AGUS rate of 0.11% to 0.74%,[2-4,6-8,11,12] although many of these reports were from primary screening centres.

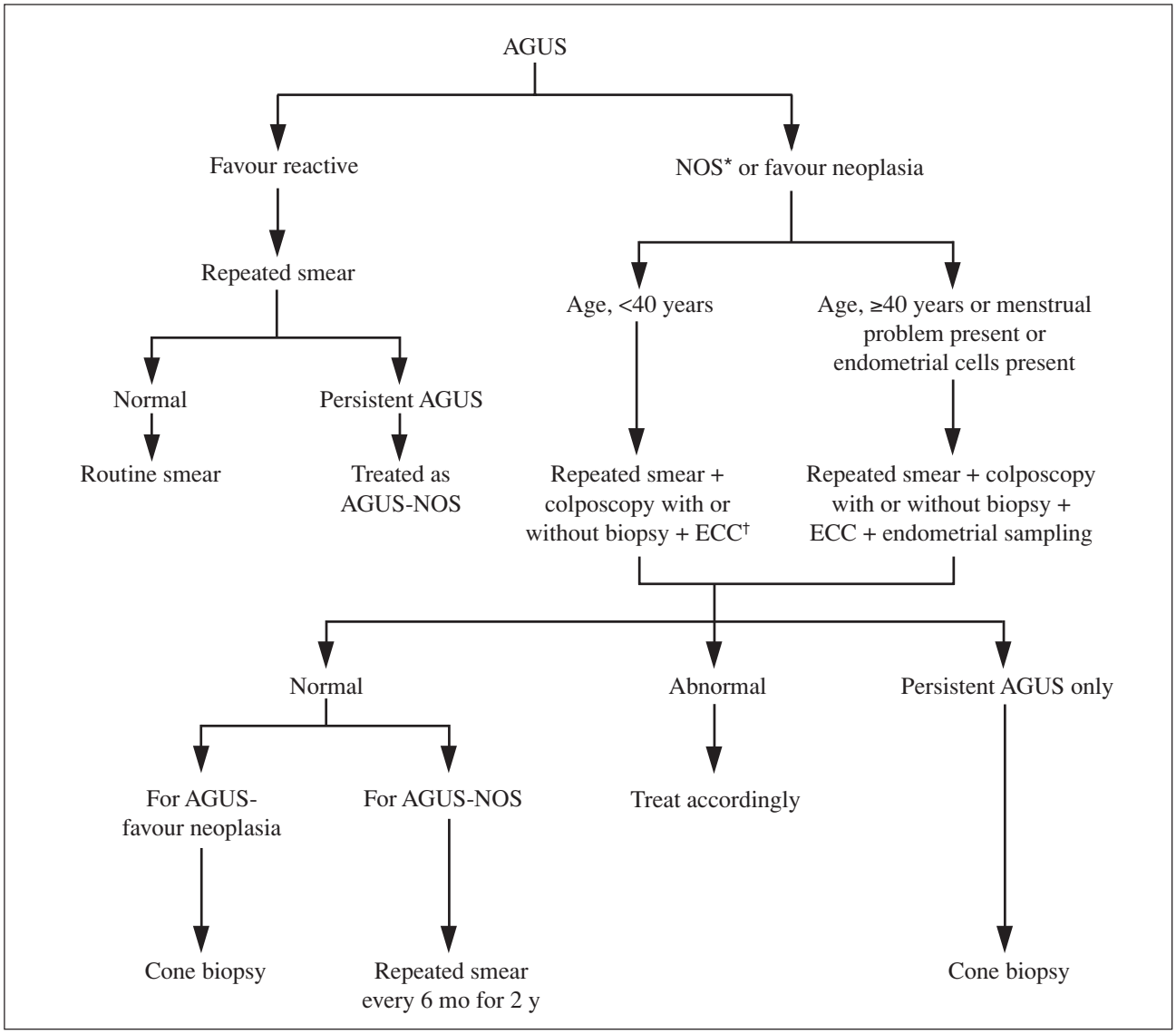
Pathologists can help in the management of AGUS cases by subclassifying them. Our study showed that among the group with AGUS-favour reactive, only one case of CIN was detected among the 13 cases. Hence, repeating cervical smear tests may be all that is necessary to detect this subtype. Actually, in the most recent revision of the Bethesda classification system in May 2001, the subtype 'AGUS-favour reactive' was deleted from the list of epithelial cell abnormalities.[13] Among the 49 cases with AGUS-NOS, 21 cases had clinically significant lesions, accounting for 43% of this subtype. There were two cases of adenocarcinoma of the cervix, two of endometrial carcinoma, one of endometrial hyperplasia, three of AIS, 12 of CIN, and one of metastatic tumour from the breast. The majority of patients with the subtype of AGUS-favour neoplasia (90%) had significant disease and six had invasive tumours. These

two subtypes must, therefore, be investigated fully and immediately.

Cone biopsy appeared to be the best investigation method, with a 100% detection rate. Two cases without cone biopsy had obvious tumour over the cervix. Colposcopy-guided cervical biopsy was also very good in identifying the significant lesions, with a detection rate of 82%. The good result was probably because there were only six cases of adenocarcinoma and the rest were associated with either CIN lesions or with other subtle abnormalities over the cervix. Most cases of AIS were detected incidentally after biopsy of these lesions. Our result stressed the importance of performing a biopsy on any suspicious lesions. Colposcopy alone seemed disappointing, detecting only four (36%) cases of endocervical lesions. Two cases had gross cancer growths and the other two small papillary-like growths over the cervix. Many studies have reported that AIS is difficult to recognise using colposcopy: many cases have no observed or non-specific colposcopic signs, or the lesion can be very small and located in the endocervical cleft or proximal endocervix.[5,6,13,14] Likewise, endocervical curettage gave a rather poor detection rate of 55%, and the tissue taken was often inadequate for a diagnosis to be made. Repeated cervical smear testing gave an unexpectedly good result of 73%. This finding might be related to the simultaneous use of an Ayre spatula and an endocervical brush for all patients with AGUS in our series. Repeated cervical smear testing should, therefore, be included in the investigation list for patients with AGUS.

For significant endometrial lesions (ie hyperplasia or carcinoma), there were six cases and all were diagnosed by endometrial sampling with or without H&C. Repeated cervical smear testing detected only a third of the patients with significant lesions. Colposcopy and

Fig 2. Management of patients with atypical glandular cells of undetermined significance (AGUS)



* NOS not otherwise specified
† ECC endocervical curettage

endocervical curettage were not useful at all in our study.

For cervical squamous lesions, it is quite obvious that colposcopy and biopsy identified most of the lesions. Endocervical curettage was not useful in detecting cervical squamous disease and it detected only 14% with significant diseases.

All patients with AGUS-qualifying endometrial cells should undergo endometrial assessment by either endometrial sampling or dilatation and curettage or H&C, because 20% of them had endometrial carcinoma. This is particularly important for patients who are older than 40 years and who have a menstrual problem. However, a colposcopy with or without biopsy should also be performed; 13% of them still had high-grade CIN lesion.

On the basis of these results, we can formulate management guidelines for patients with AGUS in a more rational manner. Such patients, if reported as having reactive disease (which should not happen now with the new classification system), can be managed by repeated cervical smear testing alone. Only when the repeated cervical smear still shows AGUS or more significant lesions, should patients be tested in detail similar to that of AGUS-NOS or AGUS-favour neoplasia. For AGUS-NOS or AGUS-favour neoplasia, all patients should undergo repeated cervical smear testing with an Ayre spatula and endocervical brush followed by colposcopy with or without biopsy, because this approach will detect most cases of endocervical glandular lesion, and almost all the cervical squamous lesions. Cervical biopsy should be done whenever there is any suspicion of abnormality. Endocervical curettage can be done immediately after the colposcopy, because it is a relatively simple and non-invasive procedure, even though its detection rate for glandular cervical lesion is not particularly high (approximately 50% in our study and in other reports[6]). Endometrial sampling or H&C should be done for patients who are older than 40 years or having menstrual problems, or if the cells are endometrial in origin. Cone biopsy should be performed if there is persistent AGUS on the smear despite normal findings from the above investigations. It should probably be done for patients with AGUS-favour neoplasia even if all the findings are negative, because 90% of these patients had significant disease in our study. The flowchart for the management of AGUS is summarised in Fig 2.

Conclusion

Atypical glandular cells of undetermined significance, other than those specified as reactive, should be investigated early and thoroughly. Tests include repeated cervical smear testing, colposcopy with or without biopsy, endocervical curettage, cone biopsy, and endometrial biopsy when indicated, because a high percentage of Chinese patients will have premalignant or malignant disease in genital tract.

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