ASCUS: comparative follow-up results related to previous SIL diagnosis

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Summary

The clinical significance of ASCUS (atypical squamous cells of undetermined significance) remains undetermined. In a variety of cases, it is possible to identify an underlying neoplastic squamous lesion. With the aim of establishing some rationale basis for management, we have evaluated the history and the follow-up of 137 woman diagnosed with ASCUS. These woman were distributed into two groups, with or without history of SIL (30 and 107 woman, respectively); 38 woman did not come to the control. In general, the rate was 30.3% for low grade SIL (squamous intraepithelial lesions) and 6.1% for high grade SIL. In both groups the rate of low and high grade SIL was similar. In our opinion, women that are diagnosed with ASCUS must be submitted to colposcopic exams independently of their history.

Key words: ASCUS; SIL; Dysplasia; Follow-up; Clinical significance.

Introduction

ASCUS (atypical squamous cells of undetermined significance) is considered to be a minor cytologic lesion whose clinical significance is not well defined. The follow-up and therapeutic attitude related to this lesion are unresolved. Some authors suggest only cytologic follow-up and others propose a colposcopic-biopsy evaluation in a specialised unit. These differences are obviously due to different valuations of this diagnosis related to dysplatic lesion development.

The aim of this paper was to investigate the natural history of ASCUS and to establish some methodologic facts about the follow-up of these patients.

Patients and Methods

We studied all HIV negative women diagnosed with ASCUS between December 1989 and June 1995. We separated the cases into two groups depending on their history. (SIL or no SIL previous diagnosis). Most patients with a history of SIL (squamous intraepithelial lesions) are diagnosed as SIL within five years prior to a diagnosis of ASCUS (although we require an interval of 18-months free of disease).

A total of 137 patients were included and their history, clinical data and follow-up were evaluated. Of these, 30 patients showed a history of low or high grade SIL, and were checked in a cervical pathology unit.

All the patients diagnosed with ASCUS underwent colposcopy, citology and cervical biopsy. The first follow-up was carried out in the first six months after the diagnosis of ASCUS, and the second check-up was carried out between six and 18 months after the diagnosis of ASCUS.

Patients with a diagnosis of high grade SIL were treated appropriately. If a high grade SIL diagnosis was made at the first control, the patient was not evaluated in the second control data.

In both groups of patients the appraisal of SIL was evaluated and compared (χ^2 test).

Results

a) Group without antecedents (107 cases): 37 of these patients did not come to the first follow-up check. In the remainder of patients (70), SIL appeared in 26 cases (37.1%) at the first or second check-up (20 cases at the first check and 6 cases at the second check). Of these 70 patients, 35 did not come to the second check; 6 of these showed SIL changes at the first check. The summary of these results are in tables I and II.

b) Group with antecedents (30 cases): 29 of these came to the first check-up. We found SIL changes in 11 of these patients (37.9%), 8 at the first check and 2 at the second check. The remaining case was a microinfiltrant carcinoma found at the first check-up. The summary of these results are in tables I and II.

The global appraisal of low grade and high grade SIL in both groups of patients was 30.3% and 6.1%, respectively, with one microcarcinoma detection. Table IV shows the main results of both patient groups. Statistically there were no significant differences in the SIL rates diagnosed in both groups.

Discussion

ASCUS is defined as the presence of cells with atypical nuclei in cervical squamous epithelium without other morphological changes that allow classification of these

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Table 1. — *Patients without antecedents. Results of the second check-up related to the results of the first one (N=70).*

RFC	Results of second check			
	NEG	MI.D	SE.D	DCU
NEG (50)	16	5	1	28
MI.D (15)	5	3	–	7
SE.D (5)	–	–	–	–

RFC: Results of first check; MI.D: Mild dysplasia; SE.D: Severe dysplasia; DCU: Did not come.

Table 2. — *Patients without antecedents of dysplasia. Results of the second check-up related to the results of the first one (N=29).*

RFC	Results of second check			
	NEG	MI.D	SE.D	DCU
NEG (20)	12	2	–	6
MI.D (8)	4	2	–	2
Carcinoma (1)	–	–	–	–

RFC: Results of first check; MI.D: Mild dysplasia; SE.D: Severe dysplasia; DCU: Did not come.

Table 3. — *Follow-up of patients with diagnosis of ASCUS. Results of the second check-up related to antecedents of dysplasia.*

	1	2	3
No. ant.	65	35/65 (53.8%)	6/22 (27.3%)
Ant.	28	8/28 (28.6%)	2/14 (14.3%)

1: Number of patients evaluated in the second check; 2: Percentage of patients that did not show up at the second check; 3: Percentage and total number of patients with dysplasia that appear in the second check with the first check negative.

Table 4. — *Apparition of squamous lesions (dysplasia).*

	TO.D	MI.D	SE.D
Total patients	37/99 (37.3%)	30/99 (30.3%)	7/99 (7.1%)
No antec.	26/70 (37.1%)	20/70 (28.6%)	6/70 (8.6%)
Antecedents	11/29 (37.9%)	10/29 (34.5%)	1/29 (3.4%)
"P"	0.94	0.56	0.66

TO.D: Total cases of dysplasia; MI.D: Mild dysplasia; SE.D: Severe dysplasia.

cells as dysplastic cells or HPV-related changed cells, obviously without infectious, inflammatory, reparative or atrophic changes [1-3]. The Bethesda System recommends that cytologists specify if these changes could represent reactive or dysplastic changes. Many cytologists think that this orientation is not feasible because of poor reproductibility and subjectivity. Nevertheless some papers have evaluated this possibility [4, 5].

In general, the main cytology laboratories do not make supplementary considerations of the diagnosis of ASCUS. However the cytologist obviously can make some considerations about a case.

The diagnosis of ASCUS is made in about 1-3% of cases in the general population. In an investigation carried out in American cytology laboratories in 1993, the diagnostic rate of ASCUS was 2.8%. However, 10% of these laboratories showed rates greater than 9% [6]. Selvaggi [7] found only 0.7%. These differences do not appear often but they could have clinical implications. In our population the diagnostic ASCUS rate is 1.2%.

The clinical significance of these cytological changes is uncertain. These changes could disappear spontaneously, but in a percentage of cases a detailed cervical evaluation (colposcopy and directed biopsy) could show the presence or posterior apparition of dysplasia (in some cases, high grade). In the American inquiry [6], the average dysplasia apparition rate in the first 12 months after diagnosis of ASCUS was 20%. This means that the dysplasia apparition rate varies from 11.9% [4] to 66.7% [9]. Melnikow [8] reported an average ASCUS spontaneous regression rate of 68.19% and an average high grade dysplasia development rate of 7.13% within 24 months after the diagnosis of ASCUS.

In the majority of series the mean high grade dysplasia is between 5 and 15%. The great variability could depend on the morphologic criteria to establish ASCUS as a diagnosis, the clinical management of these patients, and the population studied risk factors. This variability is necessary for each hospital to establish its protocol for the ASCUS cases, based on the population and the data. In general there are two trends in the literature. Cytologic follow-up [10, 11] and the systematic colposcopic evaluation with or without biopsy in a cervical pathology unit [9, 12-14]. The official entities promote evidence-based performance guides [24, 25]. Some authors have suggested evaluating clinical risk criteria [15-17]. Many authors evaluate other procedures such as cervicography [18], HPV typing [13, 19-21], or the expression of cellular proliferation markers [23] achieved very good sensitivity for the detection of high grade SIL-carcinoma, compounding an automatic informatized cytologic evaluation and HPV type, but there are no studies about the cost-benefit of this procedure.

In our data we found a high percentage of SIL related to ASCUS cytologic diagnosis, detected by other complementary techniques (biopsy conducted by colposcopy). Our percentages were similar to those reported in the literature. The majority of these cases are low grade SIL, but many cases are high grade SIL. It is possible that the follow-up must be long-term for many months because the dysplastic processes may appear later.

The dysplastic process may appear similar in frequency in the general population as in those woman with dysplastic antecedents. Therefore, the antecedent of dysplasia is not an important factor for the management of these patients.

About 30 of these patients did not come to the following check-up even with the diagnosis of dysplasia. This fact has also been observed by other authors [10] and may be due, in our patients, to some sociodemographic characteristics, such as low socioeconomic level and temporary residence. Therefore, this data leans towards the need of immediate colposcopy evaluation, and emphasizes the necessity for timely follow-up.

We think overall that in our population the diagnosis of ASCUS needs an initial colposcopic evaluation. In our

protocol, colposcopy is carried out between 3 to 6 months after the diagnosis of ASCUS.

It is very important to strictly adjust the morphologic criteria for the cytologic diagnosis of ASCUS in order to avoid over-diagnosis.

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References

[1] Solomon D., Frable W. J., Vooijs G. P., Wilbur D. C., Amma N. S., Collins R. J., Davey D. D., *et al.*: "ASCUS and AGUS criteria". International Academy of Cytology Task Force Summary. Diagnostic Cytology Towards the 21st Century: An International Expert Conference and Tutorial. *Acta Cytol.*, 1998 Jan.-Feb., *42* (1), 16.

[2] Abati A., Jaffurs W., Wilder A. M.: "Squamous atypia in the atrophic cervical vaginal smear: a new look at an old problem". *Cancer*, 1998 Aug. 25, *84* (4), 218.

[3] Howell L. P., Davis R. L.: "Follow-up of Papanicolaou smears diagnosed as atypical squamous cells of undetermined significance". *Diagn. Cytopathol.*, 1996 Feb., *14* (1), 20.

[4] Gonzalez D., Hernandez E., Anderson L., Heller P., Atkinson B. F.: "Clinical significance of a cervical cytologic diagnosis of atypical squamous cell of undetermined significance. Favoring a reactive process or low grade squamous intraepithelial lesion". *J. Reprod. Med.*, 1996 Oct., *41* (10), 719.

[5] Kline M. J., Davey D. D.: Atypical squamous cells of undetermined significance qualified: a follow-up study". *Diagn. Cytopathol.*, 1996 Jun., *14* (4), 380.

[6] Davey D. D., Nielsen M. L., Naryshkin S., Robb J. A., Cohen T., Kline T. S.: "Atypical squamous cells of undetermined significance. Current laboratory practices of participants in the College of American Pathologists Interlaboratory. Comparison Program in Cervicovaginal Cytology". *Arch. Pathol. Lab. Med.*, 1996 May, *120* (5), 440.

[7] Selvaggi S. M., Haefner H. K.: "Reporting of atypical squamous cells of undetermined significance on cervical smears: is it significant?". *Diagn. Cytopathol.*, 1995 Nov., *13* (4), 352.

[8] Melnikow J., Nuovo J., Willan A. R., Chan B. K., Howell L. P.: "Natural history of cervical squamous intraepithelial lesions: a meta-analysis". *Obstet. Gynecol.*, 1998 Oct., *92* (4 Pt 2), 727.

[9] Yang M., Zachariah S.: "ASCUS on cervical cytologic smears. Clinical significance". *J. Reprod. Med.*, 1997 Jun., *42* (6), 329.

[10] Alanen K. W., Elit L. M., Molinaro P. A., McLachlin C. M.: "Assessment of cytologic follow-up as the recommended management for patients with atypical squamous cells of undetermined significance or low grade squamous intraepithelial lesions". *Cancer*, 1998 Feb. 25, *84* (*1*), 5.

[11] Cecchini S., Iossa A., Bonardi R., Ciatto S., Cariaggi P.: "Comparing two modalities of management of women with cytologic evidence of squamous or glandular atypia: early repeat cytology or colposcopy". *Tumori*, 1997 Jul-Aug., *83* (*4*), 732.

[12] Kobelin M. H., Kobelin C. G., Burke L., Lavin P., Niloff J. M., Kim Y. B.: "Incidence and predictors of cervical dysplasia in patients with minimally abnormal Papanicolaou smears". *Obstet. Gynecol.*, 1998 Sep., *92* (*3*), 356.

[13] Ferris D. G., Wright T. C. Jr., Litaker M. S., Richart R. M., Lorincz A. T., Sun X. W., Woodward L.: "Comparison of two tests for detecting carcinogenic HPV in women with Papanicolaou smear reports of ASCUS and LSIL". *J. Fam. Pract.*, 1998 Feb., *46* (*2*), 136.

[14] Williams M. L., Rimm D. L., Pedigo M. A., Frable W. J.: "Atypical squamous cells of undertermined significance: correlative histologic and follow-up studies from an academic medical center". *Diagn. Cytopathol.*, 1997 Jan., *16* (*1*), 1.

[15] Melnikow J., Nuovo J., Paliescheskey M., Stewart G. K., Howell L., Green W.: "Detection of high-grade cervical dysplasia: impact of age and Bethesda system terminology". *Diagn. Cytopathol.*, 1997 Nov., *17* (*5*), 321.

[16] Rader A. E., Lazebnik R., Arora C. D., Franklin J., Abdul-Karim F. W.: "Atypical squamous cells of undertermined significance in the pediatric population. Implications for management and comparison with the adult population". *Acta Cytol.*, 1997 Jul.-Aug., *41* (*4*), 1073.

[17] Ghoussoub R. A., Rimm D. L.: "Degree of dysplasia following diagnosis of atypical squamous cells of undetermined significance is influenced by patient history and type of follow-up". *Diagn. Cytopathol.*, 1997 Jul., *17* (*1*), 14.

[18] Eskridge C., Begneaud W. P., Landwehr C.: "Cervicography combined with repeat Papanicolaou test as triage for low-grade cytologic abnormalities". *Obstet. Gynecol.*, 1998 Sep., *92* (*3*), 351.

[19] Recio F. O., Sahai Srivastava B. I., Wong C., Hempling R. E., Eltabbakh G. H., Piver M. S.: "The clinical value of digene hybrid capture HPV DNA testing in a referral-based population with abnormal pap smears". *Eur. J. Gynaecol. Oncol.*, 1998, *19* (*3*), 203.

[20] Autillo-Touati A., Joannes M., d'Ercole C., Robaglia-Schlupp A., Lambert A., Mazzella E., Blanc B., Seite R.: "HPV typing by in situ hybridization on cervical cytologic smears with ASCUS". *Acta Cytol.*, 1998 May-Jun., *42* (*3*), 631.

[21] Ferris D. G., Wright T. C. Jr., Litaker M. S., Richart R. M., Lorincz A. T., Sun X. W., Borgatta L. *et al.*: "Triage of women with ASCUS and LSIL on Pap smear reports: management by repeat Pap smear, HPV DNA testing, or colposcopy?". *J. Fam. Pract.*, 1998 Feb., *46* (*2*), 125.

[22] Dunton C. J., van Hoeven K. H., Kovatich A. J., Oliver R. E., Scacheri R. Q., Cater J. R., Carlson J. A. Jr.: "Ki-67 antigen staining as an adjunct to identifying cervical intraepithelial neoplasia". *Gynecol. Oncol.*, 1997 Mar., *64* (*3*), 451.

[23] Sherman M. E., Schiffman M. H., Lorincz A. T., Herrero R., Hutchinson M. L., Bratti C., Zahniser D. *et al.*: "Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing". *Cancer*, 1997 Apr. 25, *81* (*2*), 89.

[24] Duncan I. D.: "Guidelines for clinical practice and programme management". Oxford: National Co-ordinating Network, NHS Cervical Screening Programme, 1993.

[25] American College of Obstetricians and Gynecologists Committee on Quality Assessment: "ACOG criteria set. Atypical squamous cells of undetermined significance (ASCUS)". *Int. J. Gynaecol. Obstet.*, 1996 Feb., *52* (*2*), 215.

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