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ORIGINAL RESEARCH ARTICLE

Educational Needs and Causes of False Diagnosis of Atypical Squamous Cells of Unknown Significance at a University Hospital

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Abstract

The entity of atypical squamous cells of undetermined significance (ASCUS) in The Bethesda System 2001 for reporting cervical cytology is characterized by equivocal diagnosis, poor reproducibility and debatable management. This retrospective study was done to analyse the causes of false ASCUS if any and identify the educational needs as part of quality assurance programme. Cervical smears of all ASCUS cases reported over the one-year period were reviewed by the Cytopathologist. Relevant clinical data was retrieved. ASCUS was the most common type of abnormality representing 43.0 % cases among 294 abnormal smears reported during study period. 16.0% cases were found to be non ASCUS on review. The main four causes of over use of ASCUS diagnosis were poor quality smears and cellular atypia associated with Candida infection, atrophy and squamous metaplasia. Educational measures are being undertaken to avoid over diagnosis and improve the patient management (*Afr J Reprod Health 2011; 15[1]: 111-114).*

Résumé

Causes des fausses cellules de l'épithélium atypique d'un diagnostic d'une signification inconnue et le besoin éducatif dans un Centre Hospitalier Universitaire. L'entité des cellules de l'épithélium atypique d'une signification non déterminée(CEAS) dans le système Bethesda 2001 destiné à la déclaration de la cytologie cervicale est caractérisée par le diagnostic équivoque, une mauvaise reproductivité et un traitement discutable. Cette étude rétrospective a été faite pour analyser les causes des fausses CEAS, si cela existe, et d'identifier les besoins éducatifs comme faisant partie du programme de l'assurance de qualité. Le Cytopathologue a passé en revue tous les frottis de tous les cas de la CEAS qui ont été déclarés au cours d'une année. Les données cliniques nécessaires ont été rétablies. La CEAS était l'anomalie la plus commune, ce qui représente 43,0% parmi les 294 frottis anomaux qui ont été déclarés au cours de la période de l'étude. A la revue, on a découvert que 16,0% n'étaient pas des CEAS. Les quatre causes principales du suremploi du diagnostic de la CEAS étaient la mauvaise qualité du frottis et l'atypie cellulaire liée à l'infection candidose, l'atrophie et la métaplasie squameuse. On prend des mesures éducatives pour éviter le surdiagnostic et pour améliorer le traitement de la patiente (*Afr J Reprod Health 2011; 15[1]: 111-114).*

Keywords: ASCUS, Cervical smear, Pap test, False diagnosis, Atrophy, Candida

Introduction

The entity of atypical squamous cells of undetermined significance (ASCUS) in The Bethesda System (TBS) 2001 for reporting cervical cytology (also known as Pap smears) is characterized by equivocal diagnosis, poor reproducibility and debatable management.[1,2] Therefore it is a challenge to the pathologist and clinician alike and stressful for the patient.

Our cytology laboratory is attached to the University Hospital and receives Pap smears collected in outpatient departments of our hospital and those sent by clinical officers, general practitioners, physicians and gynecologists from other private hospitals, clinics and laboratories. All cases are screened initially by the residents and then reported in consultation with the faculty (two tier screening).

The present study was done to analyse the causes of false ASCUS if any and identify the educational needs for the residents and pathologists as part of quality assurance programme of our lab. The aim is to propose measures to improve the efficacy of cervical cytology screening. In Kenya, there is only opportunistic screening of the women visiting any out- patient clinic for gynecological or unrelated conditions and asymptomatic women who request it.

Methods

The laboratory records of all abnormal Pap smears were reviewed for the one-year period from January 1, 2009 to December 31, 2009. Relevant clinical data and follow up cytology or histology (where available) for all ASCUS cases was retrieved. No reflex Human Papillomavirus (HPV) testing is done in our lab. The cytopathologist

(NK) with experience of 25 years reviewed all the smears reported as ASCUS.

Results

A total of 6,500 Pap smears were screened during the study period out of which 294 (4.5%) were reported abnormal. ASCUS was the most common type of abnormal pap smear result representing 43.0 % (126) cases among all abnormal pap smears. The diagnosis of squamous intraepithelial lesion (SIL) including low grade SIL and high grade SIL was given in 30.6% (90) and 16.3% (48) cases, respectively. The remaining 10.1% (30) cases included atypical glandular cells, endometrial cells in women above 40 years of age and adenocarcinoma. The ASCUS and SIL (including low and high grade) ratio was 0.9.

The age range of women with ASCUS diagnosis was 21–63 years (mean age 32 years). Table 1 shows the distribution of all women with ASCUS diagnosis in different age groups. The maximum percentage 62.0% (78 out of 126) of women was in the age group of 30-45 years.

Age range	Number of women (%)
21-29 years	18 ((14.0)
30-45 years	78 (62.0)
45-55 years	24 (19.0)
>55 years	6 (5.0)

In 78.6% (99 out of 126) women no clinical data was available and this could include both symptomatic and asymptomatic women for routine pap smears. The clinical profile was available only in 21.4% (27 out of 126) women with ASCUS diagnosis. The previous diagnosis of ASCUS, low grade SIL and high grade SIL was available in 37.0 % (10), 14.8% (4) and 7.4 % (2) respectively. Past history of LEEP was available in 18.5 % (5) women. In addition 18.5 % (5) had presented with bleeding and 11.1% (3) had vaginal discharge. Positive HIV status was mentioned in 30.0% (8 cases) only.

On review of all ASCUS smears none of the above mentioned significant history appeared to be the cause of false diagnosis of ASCUS in our series. Only 23.8% (30 out of 126) cases were found to be non ASCUS in women with no significant past history. These were diagnosed as normal in 10.0% (3 out of 30) cases, inflammation with Candida infection in 13.3% (4) cases, atypia in atrophic smear of 20.0% (6) post menopausal, 6.7% (2) post partum women and 16.7% (5) women with prolonged use of injectable Depo provera. Twenty percent (6) were considered unsatisfactory due to poor quality smears and 13.3% (4) were immature squamous metaplasia. None of the case was upgraded to SIL or squamous cell carcinoma (SCC).

The follow-up cervical biopsy done within 2 months of Pap test was available for only 16.0% (20 out of 126) cases with initial ASCUS result. The biopsy was normal in 75.0 % (15) cases. CIN 1 was diagnosed in 15.0% (3) cases. One case each was diagnosed as CIN 3 and SCC. Pap smears of these cases were confirmed to be ASCUS on review. There was no follow up biopsy for cases considered false ASCUS on review.

Discussion

ASCUS is defined as a cellular abnormality that is more marked than those attributable to reactive changes but that quantitatively or qualitatively falls short of a definitive diagnosis of SIL. [2] On follow up ASCUS may resolve naturally or show an exuberant reactive change or SIL or SCC on cervical biopsy. The overuse of follow-up procedures may increase the expense and morbidity of unnecessary treatment.[3]

It is particularly a matter of concern in low resource settings like sub Saharan Africa having high risk populations with high incidence and prevalence of cancer cervix and HIV. The problem is further compounded by the lack of an organized screening programme, lack of trained cytopathologists and cytoscreeners and lack of facilities for HPV testing. There is fear among pathologists of missing an abnormality due to the higher prevalence of risk factors in this population, the lack of timely follow-up of abnormal pap smears in view of the opportunistic screening, the non availability of records or patient information to enable rescreening of previous pap smears. [4]

All of the above raises important quality assurance issues. It is currently recommended that laboratory rates of ASCUS should be less than 5.0 % in low-risk populations and less than 2 to 3 times the SIL rate in high-risk populations.[3] It was less than one in our study and well within the recommended range.

High risk patient profile such as HIV positive, previous ASCUS or antecedent SIL, previously treated for SIL are more likely to get an ASCUS report. [3] However in our study this did not reflect over diagnosis of ASCUS. The clinical information was not available in 79.0% women and is the main limitation of this study in addition to poor follow up information.

Educational sessions for the clinicians are being conducted and emphasis is given on the critical steps to obtain good quality smears and importance of adequate and necessary information on the laboratory requisition forms. A user friendly request form with a checklist of the minimum essential data has been developed and is now in use. Educational session was conducted for clinicians and other personnel such as nurses and residents involved in filling the request form.

Presence of air drying, thick poorly spread smear, hemorrhagic smear, superimposed or crushed nuclei and dense inflammation obscuring morphology can result in over diagnosis of ASCUS. [3,5] Upon reevaluation, ASCUS in 5.0 % (6 out of 126) of our cases should have been labeled unsatisfactory due to poor quality smears. A rescreening diagnosis of HSIL or invasive carcinoma for

a smear originally reported as ASCUS is serious error but was not seen in any of our cases.

Nuclear changes are critical for making the ASCUS diagnosis and include chromasia, chromatin texture, nuclear shape and size, and nucleolus. The squamous cell with nuclear enlargement of 2.5 to 3 times the size of intermediate squamous cell nucleus is classified as ASCUS. [2] However visual comparison of nuclear size of ASCUS from intermediate cell nucleus is imperfect with low accuracy.[6] This is an unavoidable cause of over or under diagnosis of ASCUS. Different observers give preference to different criteria and have different threshold.

The important potential implication of this study is that the causes of false ASCUS identified in this study can be avoided with educational measures that are already in place in our laboratory now. These include instructional tutorials for the pathologists and residents to use strict criteria of ASCUS and submitting for a second review to the cytopathologist for a possible ASCUS diagnosis in such cases. There is a "learning curve" which would gradually influence interpretive thresholds. Archiving of abnormal pap smears in the laboratory is improved and facilitated by manual recording of information about all abnormal pap smears and any follow up biopsy in a separate register. Upgrading of the laboratory information system to incorporate this information and facilitate easy retrieval has been recommended to the information technologist.

In our series 3.0% of ASCUS cases were reassessed as benign with Candida infection. This can happen because of the generally unrecognized spectrum of Candida-associated changes. It needs to be emphasized in educational sessions that ASCUS of inflammation and infection such as trichomonas, candida, bacterial vaginosis or viral infection can cause transient mild nuclear atypia in cervical cells. This nuclear enlargement is only twice that of an intermediate squamous-cell nucleus. In addition other features of inflammation such as intense orangophilia may be misinterpreted as keratinizing dysplasia, vacuolated cytoplasm and/or perinuclear halo may be confused with HPV effect. Diligent search should be made to identify the organisms. This guides the clinician to prescribe proper medication for the infection, without costly follow-up. [3]

Atypia in smears showing atrophic pattern due to various causes (including 6 post menopausal and 2 post natal women and 5 women with prolonged use of Depoprovera) led to over diagnosis of ASCUS in 10.3% (13 out of 126) cases. ASCUS interpretation of reparative epithelial changes (immature squamous metaplasia) is a know pitfall and was seen in 13.3% cases. In atrophy and metaplasia, the nucleus of parabasal cells may be mildly hyperchromatic with slight increase in nuclear cytoplasmic ratio (nuclear enlargement less than 3 times of ICN), but show uniform nuclear spacing, even chromatin distribution, minimal nuclear pleomorphism and pseudokoilocytosis.[7,8,9]

The recommendation in pap smear report on the use of estrogens in post-menopausal women, treatment of infection before the repeat smear, the use of reflex HPV test if affordable (only in women over 20) before referral to colposcopy can be further helpful.[10] In our hospital most often 6 monthly follow-up with pap smears is recommended in the absence of HPV testing. In high risk patients (previously abnormal smear, poor compliance, immunosuppressed women etc.) the option of immediate colposcopy and biopsy is considered. [11]

To conclude, the main four causes of over use of ASCUS were poor quality smears, atypia in Candida associated inflammation, atrophy and immature squamous metaplasia. This was accompanied by lack of adequate and necessary information on the request forms in majority of cases. The educational measures are being undertaken to increase awareness among pathologists and clinicians to improve the patient management.

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