Review Article

STANDARDIZATION OF CERVICAL/VAGINAL CYTOPATHOLOGY REPORTING : THE BETHESDA SYSTEM (TBS) FOR REPORTING CERVICAL/VAGINAL CYTOLOGIC DIAGNOSES

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ABSTRACT

The complex detection system leading to the discovery and treatment of precancerous lesions and early cancers of the uterine cervix is touched upon. By far the most difficult and underestimated component of this system is the screening and interpretation of cervical smears. Emphasis on the latest system of reporting, The Bethesda system is highlighted upon. Weaker points of the previous systems and the need for a newer system for reporting are stressed upon. The classification of the precursors of invasive squamous cancers is not easy, and various groups have advocated several schemes, none is yet perfect or universally accepted. The variation in nomenclature become less significant when the cytopathologist is a full member of a team made up of a clinician, histopathologist, colposcopist, and oncologist. As long as all members speak to each other frequently and use the same language and terminology, they will be able to determine the best treatment for the patient.

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KEY WORDS: Cervical smears; Epithelial cell abnormalities; The Bethesda system; Vaginal smears.

Introduction

The principle goal of cervical smears is not to diagnose overt clinical cancer but to detect occult small carcinomas and precancerous abnormalities that may lead to invasive cancer. The possibility of eradication of a deadly disease by identification and treatment of precancerous changes was extremely attractive and led to widespread application of vaginal and cervical smears to population screening and the PAP smear became a household term throughout the world. In about the year 1924 George N Papanicolaou [1], an American of Greek descent and Professor of Anatomy of Cornell University Medical College, USA, made an incidental observation that cancer cells derived from the uterine cervix may be observed in human vaginal smears. He presented this observation in May 1928, apparently unaware that a Romanian pathologist, Aureli Babes [2], had introduced cytological sampling of the uterine cervix for the diagnosis of cancer atleast two years earlier and had published a detailed account in April 1928. Several years later, thanks to a fortunate association of Papanicolaou with the gynaecologist Herbert Traut [3], the cytology of the female genital tract was revived and in a book published in 1943 the method was described in detail. Subsequently, several workers documented that the vaginal or cervical smears could lead to the discovery of occult cancers of the uterine cervix [4] and the non-invasive cancerous stages confined to the surface epithelium.

Cytology of Pre-Neoplasia and Neoplasia of Uterine Cervix

Ninety percent of the pre-invasive cancers or carcinomas-in-situ of the cervix are suspected; and these cancers are 100% curable reducing the morbidity and mortality resulting from invasive cancer cervix. Dysplasia and early neoplasia are usually localised in the endocervical mucosa at the transformation zone or squamo-columnar junction in the region of cervical os or in the epithelium covering the exocervix or portio vaginalis. The location varies with age, sexual activity and parity of the patient. The original Papanicolaou system of reporting PAP smears based on five classes was judged to be ill suited to the practice of preventive oncology. The numbering system has been abused and misused. The original significance of each class was so modified by pathologist that the meaning of any class has become hopelessly confusing to the clinician. This classification should never be used without a comment on its meaning. The five classes of the origi-

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nal PAP system of numbering is briefly touched upon and compared with other pathologist's concept (Table 1). Class III, especially has often served as a convenient way to hide the weakness of the cytologist.

TABLE 1
Classification by numbers

Class	Papanicolaon concepts	Other pathologists concepts
I	Abnormal cells absent	Normal or benign atypia
II	atypical benign	Benign atypia, dysplasias
III	Suspicious, including dyskaryosis	Benign atypia, dysplasias, in-situ carcinomas
IV	Cancer (fairly conclusive)	Benign atypia, dysplasias, invasive, few cells
V	Cancer (convulsive)	In-situ, or invasive with a large number of cells, invasive carcinoma only

Reagan [5] in 1953 introduced the term dysplasia and carcinoma-in-situ for preneoplastic and early neoplastic lesions that were presumed to reflect the potential for 'good' or 'worse' behaviour. Numerous surveys showed that the diagnostic system was not reproducible and that one person's dysplasia was another person's carcinoma and vice versa. Richard's [6] nomenclature-cervical intraepithelial neoplasm (CIN) introduced in 1966 encompasses all the precancerous lesions of the cervix. Several studies have shown that morphologic criteria for distinguishing cellular changes of Human Papilloma Virus (HPV) infection from those of CIN-I vary between investigators and lack reproducibility. The danger in this system is that when a mild dysplasia is called nepotistic, it will give some clinicians a green light to perform radical surgery. It does not solve the problem of differentiating between CIN I, CIN II and CIN III. Furthermore these numbers can be misused to hide ignorance or indecision.

In December 1988, the National Cancer Institute (NCI) [7,9] sponsored a workshop to address the standardization of cervical/vaginal cytopathology reports. The workshop developed a new classification designated The Bethesda system (TBS). TBS provides a uniform format and offers a standardized lexicon for cervical/vaginal cytology reports, specifically emphasizing communication of clinically relevant information. NCI sponsored a second workshop in April 1991 to assess the utilization of TBS in actual practice and to consider areas for possible improvement [8].

The general format for laboratory reports retains three elements: a statement regarding the adequacy of the specimen for diagnostic evaluation, a general categorization of the diagnosis and a descriptive diagnosis.

Adequacy of the specimen: TBS defines a fully satisfactory specimen as containing both squamous cells and endocervical or squamous metaplastic cells. These cellular elements form the microscopic basis for the assumption that the transformation zone has been sampled. Other criteria for specimen adequacy includes appropriate labelling and identifying information, relevant clinical information and adequate number of well preserved and well visualized squamous epithelial cells. Satisfactory for evaluation indicates all of the following: appropriate labelling and identifying information, relevant clinical information, adequate numbers of well preserved and well visualized scams cells and adequate endocervical/transformation zone component. A specimen is satisfactory for evaluation but limited by... if any of the following apply: lack of pertinent clinical information, poor fixation, air drying artifact, inflammation, blood etc that precludes interpretation of 50% to 75% of the epithelial cells, and absence of endocervical component. It basically means interpretation may be compromised. Specimen unsatisfactory for evaluation means any of the following: lack of patient identification, scant squamous epithelial component (Well preserved cells only 10%) of slide surface, poor fixation etc. It means specimen is unreliable for detection of cervical abnormalities.

Descriptive diagnosis: (In relation to benign cellular changes and epithelial cells abnormalities).

Infection

Trichomonas vaginalis

Fungal organism morphologically consistent with candida species.

Predominance of coccobacilli consistent with shift in vaginal flora.

Bacteria morphologically consistent with actinomyces species.

Cellular changes associated with *Herpes simplex* virus.

Reactive changes

Inflammation (typical repair)

Atrophy with inflammation (atrophic vaginitis)

Radiation

IUD

Epithelial cell abnormalities

a)Squamous cells

Atypical squamous cells of undetermined significance (ASCUS)

Low grade squamous intraepithelial lesion (LSIL)

High grade squamous intraepithelial lesion (HSIL)

Squamous cell carcinoma

b)Glandular cells

Endometrial cells, cytologically benign in a post menopausal woman

Atypical glandular cells of undetermined significance (AGUS)

Endocervical adenocarcinoma

Endometrial adenocarcinoma

Extrauterine adenocarcinoma

Adenocarcinoma not otherwise specified.

TBS and its significance

The significance of TBS is the creation of two new categories-ASCUS and AGUS and in keeping only two grades of intra-epithelial lesions namely low grade SIL and high grade SIL. A National Cancer Institute workshop suggested that a diagnosis of atypical squamous cell of undetermined significance (ASCUS) may be expected in no more than 5% of cervicovaginal smears [10]. It concluded that a higher frequency may represent overuse of the term. However they also pointed out that in high-risk population there will be a high ratio of SIL and so a high ratio of ASCUS.

ASCUS is not a categorized diagnosis but an absence of a determinate conclusion. What it intends to convey is that the sample cannot be confidently categorised as normal or abnormal usually due to insufficient qualitative or quantitative cellular change. A different term like ASCIS (abnormal squamous cells of indeterminate significance) is more appropriate [11]. Patients whose cervical cytological smears falls into the category of ASCUS may on follow-up, exhibit a wide spectrum of findings, ranging from no pathologic abnormality to frequent SIL and to invasive carcinomas in rare instances. A diagnosis of ASCUS on smears warrants careful follow-up and investigations [12].

In reference to the precancerous intra epithelial lesions, the significant thrust of the TBS is the classification of these lesions into two categories: low grade and high grade. The low-grade lesion include all the neoplastic changes previously classified as mild dysplasia, CIN I or lesions with morphologic changes suggestive of HPV infections. Terms such as koilocytosis, koilocytotic atypia and condylomatous atypia are not included in the TBS lexicon. High-grade lesions comprise all other precancerous events lesions previously classified as moderate or marked dysplasia and carcinoma-in-situ (CIN II & III). Thus, the reporting of precancerous lesions is much simplified. It was thought that using only two categories would reduce

TABLE 2

The cytology report and patient management based on TBS diagnosis [10]

Cytology	Management
Benign cellular changes	
a. infection	
e.g. Trichomonas vaginalis	Treatment of infection then rescreening as for patient with normal cytology
Herpes simplex, bacterial etc.	
b. Reactive due to inflammation, radiation, biopsy, IUD, etc.	
Epithelial cell abnormalities	
a. Squamous cells	
LSIL	Rescreening within six months
HSIL	Colposcopy and biopsy
Squamous cell carcinoma	Biopsy
b. Glandular cells	
atypical glandular cells/ adenocarcinoma	Biopsy and curettage

the present inconsistencies in terminology. The proposed terminology is related to the expected clinical behaviour of the epithelial abnormalities and is management oriented in that it includes a recommendation for the preferred follow-up procedure in an individual case.

Low-Grade squamous intraepithelial lesion (LSIL): These lesions belong to a category of superficial and intermediate dysplastic cells. There is presence of a few superficial dysplastic cells having plentiful clear translucent cytoplasm with slightly enlarged nucleus occupying less than one-third of the total area of the cell. Nuclear chromatin is finely granular, evenly distributed and only slightly hyperchromatic. A significantly higher proportion of LSIL is associated with low risk papilloma viruses and a lower risk of progression in contrast to high-grade lesions. There may be certain cases in which cellular changes fall short of a definitive diagnosis of a squamous intraepithelial lesion but exceed those attributable to reactive processes, are characterised as "atypical squamous cells of undetermined significance" (ASCUS).

High-grade squamous intraepithelial lesion (HSIL): These are usually localized in the endocervical mucosa at the transformation zone and extend into the invaginations of the columnar epithelium. They are characterised cytologically by a mixture of dysplastic and cancer cells, smears are richer in abnormal cells, there is greater variation in cell population and parabasal dysplastic cells are commonly encountered. The cell morphology reveals smaller cells of the intermediate and parabasal cell type occurring singly or in syncytial aggregates with indistinct cell borders and overlapping nuclei as seen in severe dysplasia and car-

cinoma-in situ. The nuclei in high-grade lesions are enlarged, round to oval, occupying two-third of the total area of the cell. The chromatin is finely granular. HSIL also encompasses lesions previously termed atypical condyloma.

Management : LSIL patients should have the benefit of colposcopic examination or a very close follow-up by repeated cervical smears. Inspite of the fact that 60% of such cases will regress all such cases must be followed up for the following reasons. It is impossible to know which lesion will progress and which will regress. Women with LSIL are at a higher risk for developing cancer cervix. Different follow-up protocols have been advocated : these range from a cytologic follow-up every nine to twelve months to a colposcopic guided biopsy. Follow-up cytology suffices so long as the clinician and the patients are aware of the significance of the findings and the patient can be trusted to come up for follow-up annually until the lesions regresses or progresses. After regression annual follow-up should be continued for three years (Table-I).

All cases of HSIL must receive treatment after a colposcopic biopsy has confirmed the cytology report. Therapy for HSIL may be divided into two broad categories: Local ablation (electrocautery, cryosurgery, carbon dioxide laser ablation), Excisional procedures; principle is excision of transformation zone; the procedures are large loop excision of the TZ, conization, hysterectomy [13].

Microinvasive carcinoma

Cytological diagnosis of micro invasive carcinomas cannot be reliably made. Occasional bizarre cell forms and relatively large number of cancer cells with prominent nucleoli may be seen. These smears may be termed as epidermoid carcinoma with possible invasion (microinvasion).

Invasive Squamous cell carcinoma

These lesions are generally evident on inspection of the cervix and should be diagnosed by biopsy. However a small percentage of invasive cancers either may pass unnoticed on clinical examination or may not be visible because of their location within the endocervical canal. In these situations, cytological smears may prove to be invaluable in establishing the initial diagnosis. Cell morphology reveals small round oval cells arranged in syncytial aggregates with indistinct cell borders and altered cell polarity. There is cytoplasmic orangeophilia and formation of epithelial pearls in keratinising squamous carcinoma, nuclear chromatin is hyperchromatic and coarsely granular, nucleoli being observed in less differentiated tumours. A typical glandular cells of undetermined significance (AGUS) demonstrate changes beyond those encountered in benign reactive process yet are insufficient for a diagnosis of adenocarcinoma. The diagnosis of AGUS should, if possible indicate whether the cells are favoured to be of endocervical or endometrial origin.

Adenocarcinoma

A diagnosis of Adenocarcinoma on smear examination indicates invasive tumor, which could be of endocervical, endometrial and rarely of extrauterine origin. Cell morphology reveals sheets of cells with overcrowding of nuclei, clusters of cells with three-dimensional effect and rosette forms. Cytoplasm is bubbly and pale with ill defined cytoplasmic borders, nuclei are eccentric and show significant variation in size with shift to moderate hyperchromatism, irregular chromatin, and prominent nucleoli.

Limitation of TBS

The limitations of the Bethesda system is mainly in the category of low grade squamous intraepithelial lesions (LSIL). Despite the fact that 60 percent of LSIL cases will regress all such cases must be followed up since it is impossible to predict their outcome. Follow-up requires a lot of understanding and co-operation on the part of the patient without frightening her with the diagnosis. Also the entities ASCUS and AGUS are not a categorized diagnosis but absence on the part of the cytopathologist to reach a determinate conclusion to categorize the sample as abnormal or normal and thus keeping the diagnosis in an indeterminate state.

Despite the above mentioned limitations, The Bethesda system still enjoys widespread acceptance as it is related to the clinical; behaviour of the lesions and is thus management oriented with preferred follow-up procedure.

Preventable but still not prevented is an apt statement in cervical cancer. Today the majority of our patients report in a advanced stage when all that can be offered is palliative radiotherapy. With the advent of widespread screening programmes and aggressive therapy of pre-invasive lesions we hope for an overall reduction in the morbidity and mortality due to diseases.

The Bethesda system stresses the importance of communication of clinically relevant information and has gained widespread acceptance in laboratories all over the world.

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