CYTOLOGIC CRITERIA FOR DIFFERENTIATION OF BENIGN, DYSPLASTIC AND MALIGNANT CHANGES OF UTERINE CERVIX

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INTRODUCTION

Diagnostic cytology is based upon the possibliity of separating, by visual - morphologic - criteria, benign cells from malignant ones. These criteria are subjective, even though some of them may be characterized and described verbally with some degree of accuracy. The difficulty of programming automatic screening devices with these criteria well illustrates their subjective nature.

General criteria of malignancy have been described long ago and systematized by Papanicolaou and others. They include changes in size and shape of cells (anisocytosis), nuclear-cytoplasmic ratio (N/C ratio), certain cytoplasmic characteristics, size and shape of nuclei (anisokaryosis), chromasia of nuclei and pecularities of nucleoli. It has been often stated that no single change by itself is diagnostic of malignancy; that is, there are no pathognomonic changes. Even when taken together, these criteria do not encompass the whole extent of visually appreciated changes. Patterns of chromatin distribution have been shown to play an important role in the assessment of malignancy (Nieburgs).

The advent of mass screening programs for carcinoma of the cervix has provided the opportunity to study very numerous cellular samples displaying the complete range of changes from normal epithelium to obviously infiltratrating carcinoma. The detailed study of this very broad spectrum of morphologic transformation has suggested several theories concerning the development and evolution of carcinoma of the cervix. The best known of these postulates a continuous evolution from an apparently benign epithelium to invasive malignant growth. This is illustrated in Slide #1.

Great difficulties may be experienced by the pathologist when attempting to classify all intraepithelial lesions, first because there is a continuous change and therefore a very large spectrum of alterations, each minutely different from the next; second, the semantics have long been confused and involved, each author giving new names to particular changes observed at a given moment of evolution. Because of the existing problems in terminology, the World Health Organization and the International Academy of Cytology have created special committees to suggest a nomenclature and the terms used herein are those recommended by those two bodies.

The squamous epithelium of the cervix may respond to aggression by epidermization, keratinization or architectural modifications tending towards a lesser degree of differentiation as compared to normal epithelium. The columnar epithelium, on the other hand, responds by hyperplasia and metaplasia, and/or repair. Squamous metaplasia is one of the most important phenomena observed in the cervical columnar epithelium under many different conditions (inflammation, trauma, etc.).

The columnar epithelium is first pushed out by a proliferation of reserve cells, which may be poorly differentiated ("reserve cell hyperplasia") but most frequently differentiate in the direction of squamous epithelium, which may be more or less mature. Finally, the covering layer of columnar cells is shed and the whole thickness of the epithelium takes the appearance of squamous epithelium, with its enhanced protective function. Even when not maturing as well as exocervical or vaginal squamous epithelium - because it often lacks the capability of responding to the gonadal hormonal stimulation - metaplastic epithelium nevertheless displays morphological criteria of benignity: low N/C ratio with ample cytoplasm, regular round or oval nuclei with smooth contours and even membrane, small regular nucleoli, euchromasia, etc. The architectural organization is orderly, with a palisading basal layer and cells enlarging evenly towards the surface. There may be keratinization.

The next step in the evolution - if the aggressive stimuli continue acting - will be a progressive loss of orientation and differentiation of the epithelium with appearance of cellular changes: diminution of the N/C ratio, anisokaryosis (mainly by enlargement of some nuclei).

Beyond inflammation, repair and squamous metaplasia, the earliest change has been termed mild dysplasia. Although somewhat disorderly, there still is a considerable maturation of the epithelium. In moderate dysplasia, maturation is much less evident. In both mild and moderate dysplasia, the N/C ratio is only slightly increased. Nuclei are regular; the nuclear membrane is smooth; there is some variation in size of nuclei; chromasia is not increased; chromatin is either homogeneous, finely granular or reticular; and there are medium sized, regular nucleoli. In moderate dysplasia, the cells may look immature at scanning power and may bring to mind one of the definitions of carcinoma in situ, namely that "the whole thickness of the epithelium is replaced by immature cells." Immaturity, however, is not equal to malignancy and in moderate dysplasia all the cellular morphological criteria point towards a lesion that has not - as yet - developed any malignant features. Abundant cytoplasm and lack of nuclear criteria of malignancy clearly differentiate this lesion from the carcinoma in situ group.

The next very important step is an intraepithelial lesion called severe dysplasia. Here also the cells are immature and there may be a disorderly orientation of the cells in the epithelium. The N/C ratio is clearly higher than in moderate dysplasia. But the most important changes are found in the nucleus: there is hyperchromasia, anisokaryosis and the nuclear membrane is indented or irregular and unevenly thickened. Nuclei are generally not enlarged. There usually are no nucleoli and the chromatin is darkly stained, dense and often displays a sieve-like appearance under high power of the microscope, due to small circular areas surrounded by curved chromatin bands (Nieburgs). This lesion is very similar to carcinoma in situ and may precede it by a few months or years.

In carcinoma in situ there is also usually a poor maturation and disorderly polarity of the cells. The N/C ratio is high, and nuclei display hyperchromasia and anisokaryosis. The nuclear membrane is thickened, irregular and often indented. The chromatin is unevenly distributed, with prominent, irregular chromocenters connected by straight, deeply stained chromatin bands of irregular thickness and length. There are usually no nucleoli.

Early or "micro"-invasion: It is often noted that in early stromal invasion the groups of cells that actually invade are more differentiated than the surface lesion itself, sometimes becoming keratinizing with "pearl" formation. Characteristically, the cells of early invasion become larger, with larger nuclei. The nuclear membrane is irregular, but chromatin may be homogeneous or granular, or remain unevenly distributed as in carcinoma in situ. Nucleoli reappear, small at first, but growing larger with advancing invasion. Early invasion must be differentiated from gland involvement. Often the area of invasion is surrounded by a dense lymphocytic infiltrate.

In deeply infiltrating squamous carcinoma, it is possible to distinguish a differentiated type, with keratin production and an undifferentiated type which may be formed by either large or small cancer cells (Wentz and Reagan).

This description corresponds to the "continuous progression" concept.

Another school of thought considers that there are at least two different types of intraepithelial changes. One is localized mainly on the squamous epithelium of the exocervix (pars vaginalis) and tends to be well differentiated, often keratinized and mild-looking. This lesion, often interpreted as mild dysplasia, would invade without any further de-differentiation. The other type is situated in the endocervical canal. It begins as a metaplasia, becomes progressively de-differentiated and finally takes the appearance of the "classical" type of carcinoma in situ - that is, a complete replacement of the whole thickness of the epithelium by undifferentiated malignant cells. When it becomes invasive, this lesion gives rise to the undifferentiated, non-keratinizing, infiltrating carcinomas.