LOOK-ALIKES IN GYNECOLOGIC CYTOLOGY

Revised Second Edition

Marluce Bibbo, M.D., Sc.D., F.I.A.C.
Professor of Pathology and of Obstetrics and Gynecology
Section of Cytology
University of Chicago
Chicago, Illinois

and

George L. Wied, M.D., F.I.A.C.
The Blum-Riese Professor of Obstetrics and Gynecology
and Professor of Pathology
Chief, Section of Cytopathology
University of Chicago
Chicago, Illinois

INTRODUCTION

The following outline has been prepared to illustrate the "look-alikes in the cytology of the female genital tract," i.e., potential cytodiagnostic problems that may occur in the cytologic evaluation. It summarizes the salient diagnostic features of conditions presenting macronucleoli, keratinized cells, bare nuclei and elongated cells. In addition, the conditions simulating follicular cervicitis, dysplasia, carcinoma *in situ*, invasive squamous carcinoma and adenocarcinoma are presented.

I. MACRONUCLEOLI

Many conditions of the female genital tract are characterized by the presence of macronucleoli in the cytologic specimens: reparative changes, squamous carcinoma of the uterine cervix, radiation effects on benign epithelial cells, primary and metastatic adenocarcinomas, cervical decidual reaction and pemphigus. In addition, inclusion bodies in viral infections and inspissated mucus in postmenopausal atrophy may resemble macronucleoli (Slide 1). The differential diagnosis presents no problem in the majority of cases.

In reparative changes, the cells occur in clusters, and there is abundant cytoplasm, which may resemble squamous, columnar or metaplastic cells, depending on the origin of the repair. The chromatin is usually finely granular, and the nucleoli are large, round or oval, and sometimes multiple. A certain degree of anisocytosis and anisonucleosis, as well as mitotic figures, may be present (Slides 2, and 3).

In squamous carcinoma of the uterine cervix, particularly in those of the nonkeratinizing type, the cells may occur isolated or in syncytial masses. There is marked polymorphism, the chromatin is coarsely granular, and the nucleoli are large, irregular in shape and may be multiple (Slide 4).

Macronucleoli usually appear in benign epithelial cells as an effect of ionizing radiation. A history of radiation therapy and the presence of radiation cell changes, such as cellular enlargement, multinucleation, hypochromasia, pyknosis and karyorrhexis should lead to the correct diagnosis (Slide 5).

Adenocarcinomas, especially the poorly differentiated lesions, exhibit macronucleoli. Other features include cluster formation, vacuoles in the cytoplasm and coarsely granular chromatin. Metastatic adenocarcinomas may also exhibit macronucleoli. In addition to the general features of adenocarcinoma cells, group formation and lack of tumor diathesis are valuable clues for the diagnosis of metastatic adenocarcinoma (Slide 6).

Sarcomas are characterized by super nucleoli (Slide 7). Other cytologic features include lacy and poorly defined cytoplasm and a fine chromatin distribution.

Large stromal cells, singly or in clusters, characterize cervical decidual reaction. The cytoplasmic membrane is smooth and round, and the nuclei exhibit abundant chromatin detail and prominent nucleoli (Slide 8). In degenerated cells, the chromatin becomes condensed and pyknotic or may attain a bland and structureless appearance.

The parabasal or intermediate squamous cells in cell samples of cases with pemphigus vulgaris may be enlarged and pleomorphic; the nuclei exhibit vesicular or coarsely granular chromatin with single or multiple nucleoli. The bullet shape of the nucleoli is of diagnostic importance (Slide 9).

In viral infections, the eosinophilic nuclear inclusion bodies are surrounded by a large halo (Slide 10). In contrast, macronucleoli are not surrounded by halos.

In cell samples of some postmenopausal patients, parabasal cells are sometimes covered by inspissated mucus. The central core of this mucus may simulate a macronucleolus. However, the presence of the atrophic cell pattern may assist in the correct identification of the nature of the process (Slide 11).

II. KERATINIZED CELLS

Cellular keratinization of varying degrees may occur in the following cells or conditions: anucleated squames, normal pearl formations, parakeratosis, dyskeratotic cells in menopause, cells from condyloma acuminatum, keratinizing dysplasia, carcinoma *in situ* or keratinizing carcinoma of the uterine cervix (Slide 12).

Anucleated squames, i.e., mature squamous cells without nuclei, may be found in the cytologic sample from the female reproductive tract either (1) in cases of hyperkeratosis of the uterine cervix or (2) when the smear was prepared on the distal portion of the female genital tract or (3) when the specimen was taken from a pregnant patient whose fetal membranes had ruptured. In the latter case, the anucleated squames derive from the epidermis of the infant. Anucleated cells are usually flat or shrunken, and the cytoplasm may stain orange, yellow or red (Slide 13).

Benign epithelial pearls are concentric structures, usually containing keratinized cells with nuclei still visible (Slide 14).

In parakeratosis, there is a variable number of small cells with pyknotic and hyperchromatic nuclei and cytoplasm containing prekeratin or keratin (Slide 15).

The term "keratinizing dysplasia" is applied to dysplastic cells exhibiting keratinized cytoplasm. Usually the cells are differentiated; the nucleus is always enlarged and hyperchromatic (Slide 16).

Some cases of carcinoma *in situ* may exhibit keratinized cells, especially in postmenopausal patients. The presence of small round cells, with enlarged and pyknotic nuclei surrounded by orangeophilic cytoplasm, is an important clue for the diagnosis (Slide 17).

In keratinizing uterine carcinoma, there is a predominance of relatively large abnormal cells with a high degree of pleomorphism and caudate or elongated cells. The chromatin is coarsely granular, and nuclear degeneration characterized by an opaque nuclear mass is a distinct feature. The cytoplasm may be eosinophilic or orangeophilic (Slide 18). Thick plaques of anucleated squames may be the only clue for the presence of a squamous carcinoma. The outline of these plaques is irregular or jagged

Dyskeratosis is a premature keratinization of immature cells of the squamous epithelium. This process can involve the atrophic squamous epithelium of the vagina in postmenopausal patients. In these cases, the parabasal cells exhibit an orangeophilic cytoplasm (Slide 19).

Keratinized cells also occur in inflammatory reactions and should be distinguished from keratinized dysplastic cells. The inflammatory background and the polychromasia or reddish color of the cytoplasm are usually features of inflammation (Slide 20).

Degenerated endocervical cells may show orangeophilia, thus simulating keratinization (Slide 56).

III. BARE NUCLEI

Endocervical cells (especially when degenerated), autolytic cells in postmenopausal atrophy, cells from dysplasia of the uterine cervix, carcinoma *in situ* (large cell type), non-keratinizing carcinoma of the uterine cervix, endometrial or endocervical adenocarcinomas and metastatic lesions may exhibit bare nuclei in the cytologic specimen (Slide 21).

Bare nuclei are not diagnostic per se since they usually occur as a result of cellular degeneration. However, by assessing the well-preserved cells in the vicinity of the bare nuclei, one should be able to determine from which cell types the present bare nuclei originated. If they seem to have originated from normal endocervical epithelium, other well-preserved endocervical cells will be in the vicinity. In cases of autolytic cell patterns in postmenopausal atrophy, some well-preserved parabasal cells will be present. The same holds true for dysplastic cells, or cells from carcinoma *in situ*. In cases of nonkeratinizing carcinomas, isolated cells or syncytial masses of relatively large squamous cells with coarse and hyperchromatic chromatin and macronucleoli will be found, while in cases of primary endometrial or endocervical adenocarcinoma or metastatic adenocarcinoma, cells with features of adenocarcinoma (ee page 8) will be present (Slides 22 to 27).

One can usually make a judgement on the chromatin structure, even of bare nuclei, as to whether or not one is dealing with normal cells. In Slide 22, the chromatin is finely granular, suggesting the presence of a benign condition, whereas in the nuclei shown in Slide 26, macronuclei are present and the chromatin is coarsely granular, features that are compatible with an abnormal condition.

IV. MULTINUCLEATED CELLS

Multinucleation is a cytomorphologic feature commonly found in the following cells or conditions: in giant histiocytes, in syncytiotrophoblasts, in cases with folic acid deficiency, in cells affected by ionizing radiation, in metaplastic cells, in dysplastic cells, in cells from squamous carcinoma of the uterine cervix and in cells exhibiting effects of viral infections (Slide 28).

Giant histiocytes may be observed in cell samples from patients with inflammatory reactions and in smears from menopausal and postmenopausal