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Cervical Glandular Intraepithelial Neoplasia (CGIN)

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1. Introduction

Invasive adenocarcinoma is the second most common malignancy of cervix (after squamous cell carcinoma) and accounts for about 15–25% of all cervical cancers (Hopkins & Morley, 1991). The pre-invasive lesion of the adenocarcinoma of cervix which diagnosed as a spectrum of changes has been named cervical glandular intraepithelial neoplasia (CGIN). Over the past several decades, the incidence of cervical adenocarcinoma as well as its relative proportion to squamous cell carcinoma has been increasing. In 1950s and 1960s, adenocarcinoma accounted for only 5% of all invasive cancers of cervix, however it was increased and responsible for 10-22% in 1990s (Hopkins & Morley,1991; McCluggage,2000; Zaino, 2000, 2002; Wang et al.,2004; Leminen et al.,1990).

This increment may be representing both a real and an apparent increase due to a reduction in the number of invasive cervical squamous carcinomas as a consequence of organized screening programs. There also may be due to better recognition of adenocarcinoma and dysplastic endocervical glandular lesions by pathologists and appreciation of the fact that some poorly differentiated carcinomas may be glandular rather than squamous in type (revealed by the use of ancillary staining), therefore favors a real increase in the incidence of adenocarcinoma in women below 35–40 years of age (McCluggage, 2000).

The pre-invasive lesions of cervical adenocarcinoma are a heterogeneous group with various histomorphological patterns which may be confused with a wide range of non-neoplastic glandular lesions; therefore it is imperative to recognizing these presumed precursors as well as knowledge of their differential diagnosis.

This chapter focuses on an overview of the different terminology, various histopathological features, ancillary diagnostic techniques, and practical diagnostic approach to cervical glandular intraepithelial neoplasia.

2. Precursors glandular lesion of the uterine cervix

2.1 Definition

Cervical glandular intraepithelial neoplasia (CGIN) is a spectrum of presumed pre-invasive (or preneoplastic) cervical glandular lesion. The term 'presumed pre-invasive' is used

because there is some controversy as to whether these lesions, especially at the lower end of the spectrum, progress to adenocarcinoma (McCluggage, 2000). The concept of histological recognizable pre-invasive form of adenocarcinoma was at first suggested by Friedell and McKay in 1953. They have proposed that like other organs such as breast, stomach, bronchus, skin and also squamous cell carcinoma of cervix, adenocarcinoma of cervix could have these precursor lesions. Subsequent investigation was renewed interest in characterizing precursor lesions of invasive adenocarcinoma with intent to invoke a unifying theory of a common subcolumnar reserve cell for all types of cervical cancer or to categorize lesions in a fashion analogous to precursors of squamous cell carcinoma of the cervix (Zaino, 2002; Christopherson, 1979). Smedts et al. had reported that cervical intraepithelial neoplasia (CIN), combined adenocarcinoma in situ (AIS) / CIN, and a part of the solitary AIS lesions share a common, marker phenotype comparable with that endocervical reserve cells, which is indicate of a common origin. However, a second group of solitary AIS lesions with an endocervical phenotype possibly originate from a luminal type progenitor cells, within the endocervix (Smedts et al., 2010). Although endocervical adenocarcinoma in situ (AIS) is a known precursor of invasive adenocarcinoma, there is no universally accepted precursor lesion of AIS itself (Ioffe et al., 2003).

2.2 Classification and terminology of pre-invasive cervical glandular lesions

There is no consensus about the terminology using for the classification of pre-invasive endocervical glandular lesions. The term of adenocarcinoma in situ (AIS) as a precursor lesion of adenocarcinoma of uterine cervix was first described by Friedell and McKay in 1953 and most subsequent studies used this terminology (Friedell & Mckay, 1953). Other terms used to describe pre-invasive endocervical glandular lesions include *endocervical glandular dysplasia*, *cervical intraepithelial glandular neoplasia*, *cervical glandular atypia*, *endocervical columnar cell intraepithelial neoplasia* and *atypical endocervical hyperplasia*.

The International Society of Gynecological Pathologists under the auspices of the World Health Organization (WHO) included categories of glandular atypia, atypical hyperplasia (glandular dysplasia), adenocarcinoma in situ and invasive adenocarcinoma in its classification (McCluggage, 2000; Kurman, 2010).

In WHO classification, 3 categories were introduced: *1-Glandular atypia:* which refers to nonneoplastic changes often associated with inflammation; *2-Atypical hyperplasia (glandular dysplasia):* which refers to intraepithelial glandular neoplasia that is less severe than AIS and *3- AIS* (Kurman,2010).

Cervical glandular intraepithelial neoplasia (CGIN) : which is a three-tier grading system *(CGIN 1, 2 and 3)*similar to that used for pre-invasive cervical squamous lesions, that originally has been introduced by Gloor and Hurlimann (Gloor & Hurlimann,1986).This three-tier grading system was performed according to cytohistological criteria including nuclear abnormality, presence of mitosis, amount of intracellular mucin and architectural abnormality. Following this grading a new terminology was introduced by a working party of the Royal College of Pathologists and the NHS Cervical Screening Program in the Britain (NHS Cervical Screening Programme [NHSCSP], 1999). Because of difficulties in three-tier grading, particularly the distinction between CGIN 1 and 2, most authors therefore recognize only two grades of CGIN, termed high grade and low grade CGIN. This does not mean that

CGIN is a two stage disease but reflects the fact that differentiation into three grades is probably poorly reproducible. Alternatively high grade and low grade CGIN may be designated as AIS and glandular dysplasia, respectively (McCluggage, 2000).

The Silverberg group (Ioffe et al.,2003) introduced the Silverberg scoring system for assessment of the endocervical glandular lesions that is designed to aid in diagnosis and to bring about better inter- and intra observer agreement in this difficult area (McCluggage, 2000; Liang et al.,2007). This scoring scheme is based on 3 separately graded components: nuclear stratification, nuclear atypia, and mitoses/apoptosis. The scores for which are added to result in the total score equivalent to a diagnostic category: benign (score = 0-3), endocervical glandular dysplasia (score = 4-5), and adenocarcinoma in situ (score = 6-9) (Table 1) (Ioffe et al., 2003).

Stratification
-None = 0
-Mild = 1
-Moderate = 2
-Up to the luminal surface = 3
Nuclear atypia
-As normal = 0
- Small (size of normal) or slightly enlarged uniform nuclei,
 minimal hyperchromasia, little dispolarity, no nucleoli = 1
-Nuclear enlargement (up to 3 × normal), moderate anisocytosis,
 moderate hyperchromasia, moderate dispolarity, occasional small nucleoli = 2
-Large nuclei (>3 × normal), marked anisocytosis, marked hyperchromasia,
 severe dispolarity, frequent prominent nucleoli = 3
Mitoses and apoptosis
[In two most active glands, number per gland (average between two glands)]
-None= 0
-Less than 0.5 per gland = 1
-0.6–3.0 per gland = 2
- >3.0 per gland = 3
Total score
0–3 = benign
4–5 = endocervical glandular dysplasia (EGD)
6–9 = adenocarcinoma in situ (AIS)

Table 1. Silverberg group's scoring system for assessment of the endocervical glandular lesions

2.3 Pathogenesis

Among a variety of factors investigated, including the absence of a prior Pap smear, number of sexual partners, age at first intercourse, history of genital infections, obesity, and tobacco use, two conditions have emerged as potential risk factors in the development of cervical adenocarcinoma: Human Papilloma Virus (HPV) infection and oral contraceptive (OCP) use (Zaino,2000). But from different descriptive epidemiological observations, it has been suggested that adenocarcinoma may differ in pathogenetic mechanisms and that its etiology should be investigated with reference to hormonal, rather than infectious, aspects (Parazzini

et al., 1988). Ursin et al. reported that the highest risk was for oral contraceptive use for more than 12 years. No additional increased risk was found for early age at start of oral contraceptive use, use before age 20 or before first pregnancy, time since first use, time since last use, or particular formulations, once total duration of use had been accounted for (Ursin et al., 1994).But in the study by Parazzini et al., oral contraceptive use was not related to the risk of adenocarcinoma of the cervix (Parazzini et al., 1988; Madeleine et al., 2001).

Although morphologic evidence of productive HPV infection is generally limited to squamous or transitional epithelium, now overwhelming data supports the high frequency of HPV infection in both AIS and invasive adenocarcinoma (Madeleine et al., 2001; Bulk et al., 2006). In early 1980s wart viruses were not found in many of the in situ and invasive adenocarcinoma of the cervix, but with more sensitive techniques, HPV type 16, 31, and more frequently 18, have been identified in 80% and more of adenocarcinoma and adenosquamous carcinoma (Zaino, 2000). Recent studies have shown that HPV type 18 and 16 are the most common types which are detected in 43% and 23% of CGIN, respectively (Zielinski et al.,2003; Pirog et al.,2000).

2.4 Clinical signs and colposcopic features

The early diagnosis of glandular lesions still represents a real challenge for clinicians, who are likely to miss the lesions because of the absence of clinical indicators, normal cytology, or cytology suggestive of squamous disease and/or because of unfamiliarity with the diseases newly delineated colposcopic presentations.

For identifying pre-invasive cervical glandular lesions, colposcopy has not been helpful since colposcopic features of AIS and early adenocarcinoma are widely seen as known nonspecific and also this is because the disease only slightly changes the surface contour and because the neoplastic "glands "are often buried beneath the surface (Campion, 2010; Wright, 2002).

Usually most glandular lesions lie within or close to the transformation zone. While the majority of squamous lesions are usually visible by colposcopic examination, AIS may locate proximally, involving the endocervix, or may lie under the metaplastic epithelium or placed in an abnormal transformation zone and thus be out of colposcopic view (Campion, 2010; Wright, 2002).

Because of AIS coexists with high grade CIN in 30%-70% of cases and the location of the lesion, the abnormal smear will frequently predicate only the squamous lesion (van Aspert-van Erp et al.,2004). In mixed conditions that AIS and squamous cell lesions are concomitantly present, cytologic examination may only exhibiting squamous abnormality that mislead the colposcopist to look exclusively for a squamous lesion and to be satisfied upon finding it. Furthermore, the colposcopic biopsy may confirm the squamous lesion, with AIS being detected only on a subsequent wide excision or within a hysterectomy specimen. Diagnostic excisional biopsy must be always performed when AIS is found on punch biopsy or when AIS is suspected cytologically or colposcopically but not proven histologically (Campion, 2010).

Commonly colposcopic diagnosis of glandular lesions is less than satisfactory because have no specific appearance and mostly mimic the other lesions.

However, to overcome this problem a new set of colposcopic criteria has been recommended for differentiation between glandular lesion and metaplasia, condyloma, squamous intraepithelial neoplasia and squamous cell carcinoma.

The criteria are:

- Lesion locatied over columnar epithelium, not contiguous with the squamocolumnar junction;
- Large "gland" or crypt openings;
- Papillary structure;
- Budding;
- Patchy red and white coloration;
- Waste-thread, tendril, root, and character-writing blood vessels;
- Single or multiple dots produced at tips of papillary projection by looped vessels (Wright, 2002; Ostör et al., 1984).

Some features can be used to eliminate a lesion from consideration, such as punctuation and true mosaic pattern (which are present only in squamous intraepithelial lesions) and corkscrew vessels (which are associated only with invasive squamous disease).

Although many colposcopically recognized features are common to a variety of diseases, paying attention to surface contour and vascular configurations can greatly help the colposcopist discover glandular disease when it is present and differentiate it from other conditions (Wright, 2002).

2.5 Morphological features

2.5.1 Histopathological features of cervical glandular intraepithelial neoplasia (CGIN)

Adenocarcinoma in situ (AIS) of the cervix has no distinguishing clinical and colposcopic features, and because it is rare, pathologists may not be familiar with its microscopic appearances. It is easily overlooked since it may be focal and because it is frequently associated with cervical intraepithelial neoplasia (CIN), which is more impressive. There is little information about its natural history (Ostör et al., 1984).

Although there are several proposed classifications and terminologies used for describing CGINs, in most of them the morphologic criteria are nearly the same with small differences, set them in a wide spectrum between the reactive/benign lesions and invasive carcinoma in two extremities of classification.

By using these diagnostic criteria, identification of high grade lesion has been more reproducible than low grade , but most often the diagnosis of low grade lesion resulted in a confusing state of affairs for pathologists and clinicians. In most instances high grade CGIN (HCGIN) is diagnosed more often than low grade CGIN (LCGIN) in contrast to some earlier studies that reported low grade CGIN was more common (Brown, 1986).

There is a popular misconception among pathologists and gynecologists that CGIN often occurs in upper parts of the endocervical canal. However, in most, but not all cases, CGIN occurs close to the transformation zone (McCluggage, 2003). CGIN is commonly associated with a concomitant squamous intraepithelial lesion and may affect the surface epithelium and/or endocervical crypts, usually in the region of the transformation zone (Bekkers et al., 2003).

Another popular misconception is that skip lesions are extremely common in CGIN. Skip lesions undoubtedly do occur but these are relatively uncommon, probably occurring in up to 15% of patients (McCluggage, 2003).

Both high and low grades CGIN are characterized by a combination of cytological and architectural features. These features are more pronounced in high grade CGIN but not all are necessarily present in a given case of CGIN (McCluggage, 2000).

The recognition of low grade CGIN is more problematic and this lesion easily underdiagnosed by pathologists. Low grade CGIN has many overlapping features with reactive changes. Dysplastic changes in low grade CGIN are not fulfill the diagnosis of high grade CGIN and qualitatively less severe than high grade CGIN. The most common changes are: glands composed of pseudostratified cells that slightly loss their polarity, with large and hyperchromatic nuclei and minimal mitosis and apoptotic bodies. Usually stroma lacks any inflammatory or reactive changes (NHSCSP, 1999) (Figure 1- A and B).
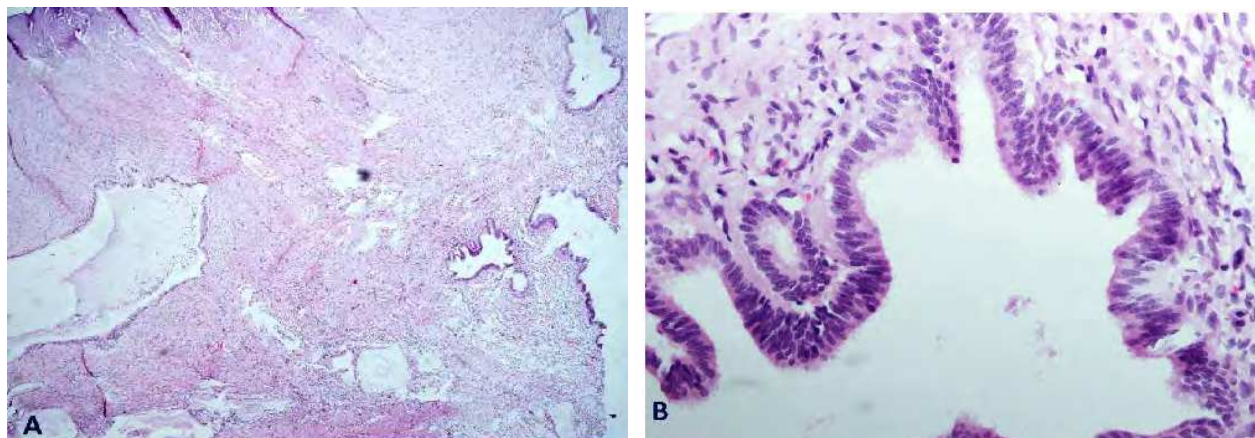

Fig. 1. LCGIN. **A,** Normal crypt in the left comparable with darker epithelium of LCGIN in the right in low magnification. **B,** Partially pseudostratified epithelium, crowded nuclei, and occasional mitotic figures are seen in higher magnification.

In high grade CGIN which abruptly begins beside the normal columnar cells (Figure 2- A and B) dysplastic changes are more severe and characterized by usually crowded glands (Figure 2- C) with various architectural patterns like budding and branching (Figure 2- D), exophytic papillae (Figure 3-A), intraluminal papillary projections (Figure 3-B) , micropapillae (Figure 3-C) and cribriform (Figure 4-A and B) , that composed of atypical cells that variably loss their cytoplasmic mucin, and display large pleomorphic

hyperchromatic nuclei with lack of polarity and easily finding mitoses and apoptotic bodies (Figure 4- C and D)(For detailed definition of histopathological features see Table 2).Glands are commonly surrounded by a compact stroma (NHSCSP, 1999).
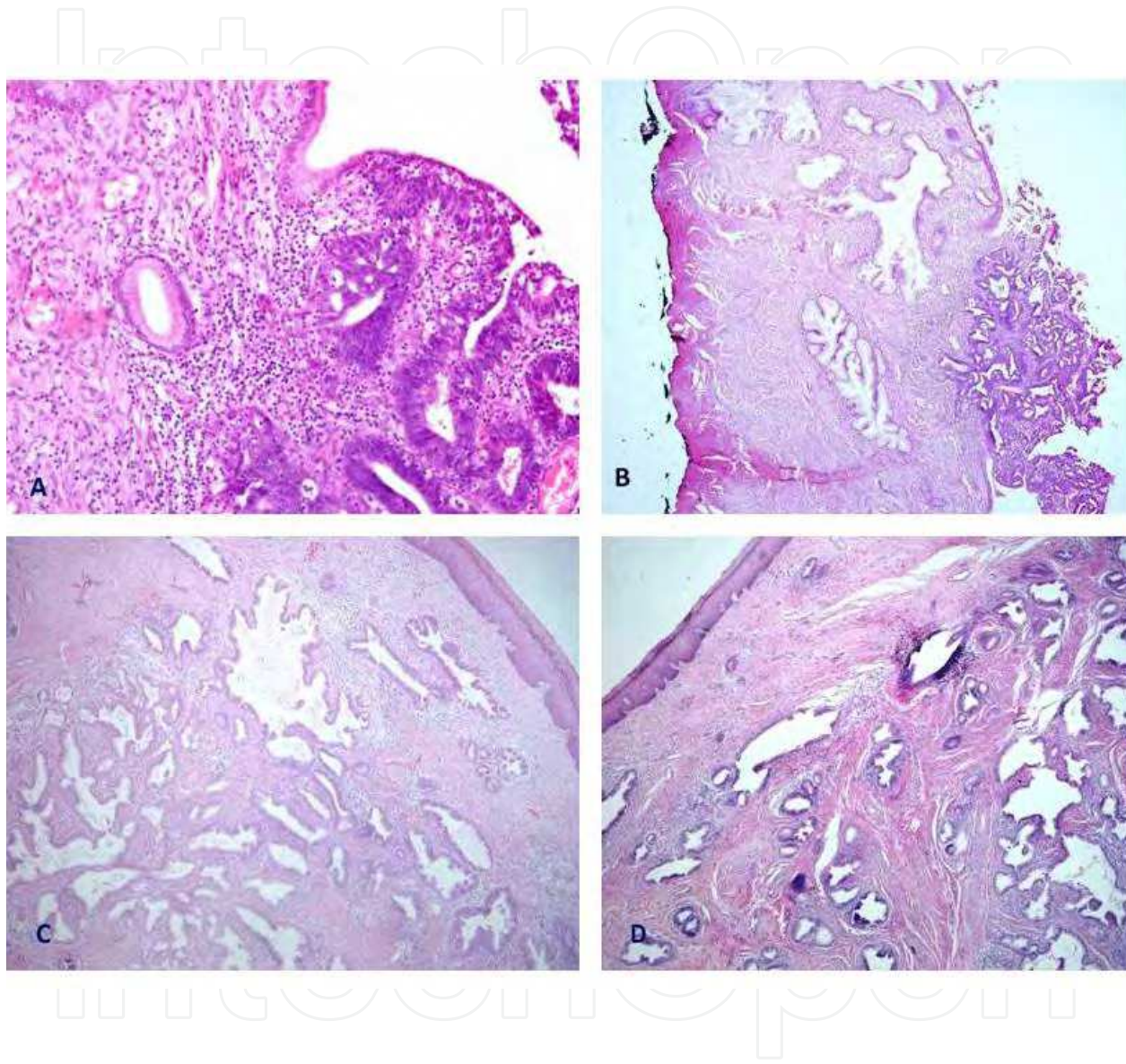

Fig. 2. HCGIN. **A,** Abrupt transition from normal endocervical columnar epithelium (top & left) to the stratified epithelium of the CGIN (right). **B,** Abrupt transition from normal endocervical columnar epithelium (top) to the stratified epithelium of the CGIN (center). **C,** A cluster of closely packed glands with branching, out-pouching and occasional in-folding. **D,** A cluster of glands with branching (irregular contour).

High grade CGIN displays three common histological subtypes: endocervical, endometrioid and intestinal as well as several uncommon subtypes: serous, clear cell, adenosquamous, villoglandular and tubal (McCluggage, 2000; Zaino, 2000).

Among them the endocervical HCGIN (alone or admixed with other types) is the most common type which mimic the normal endocervical glands. In contrast to endocervical type that small to moderate amount of cytoplasmic mucin present in luminal side of atypical cell, in endometrioid HCGIN which cells mimic the proliferative endometrial cells, their eosinophilic cytoplasm lack any mucin. Another characteristic feature in this type is significant nuclear pseudostratification. Intestinal HCGIN is recognized by its prominent goblet cell and occasional neuroendocrine or paneth cells. There is no evidence that behavior of the different subtypes of HCGIN is significantly differed (McCluggage, 2000; Zaino,2000,2002; Wang et al., 2004; Gloor & Hurlimann,1986; NHSCSP, 1999; Brown & Wells,1986; Gloor & Ruzicka,1982; Kurian & al-Nafussi,1999).
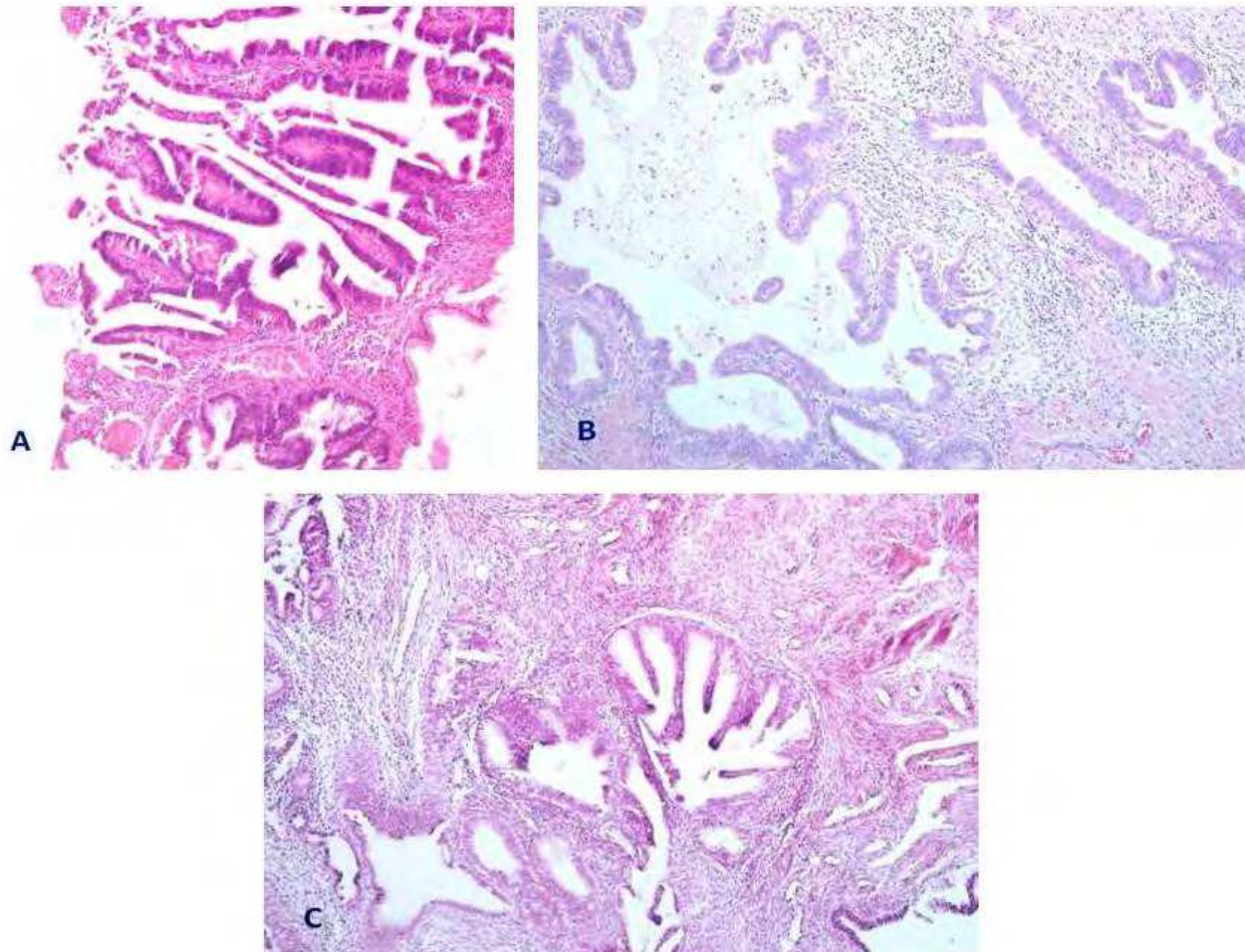

Fig. 3. HCGIN. **A,** Simple exophytic papillary pattern with thin delicate stromal stalk.
B, Infolding of epithelium into the glandular lumina with supporting stroma.
C, Intraluminal exuberance and delicate micropapillary projection with no supporting stroma.
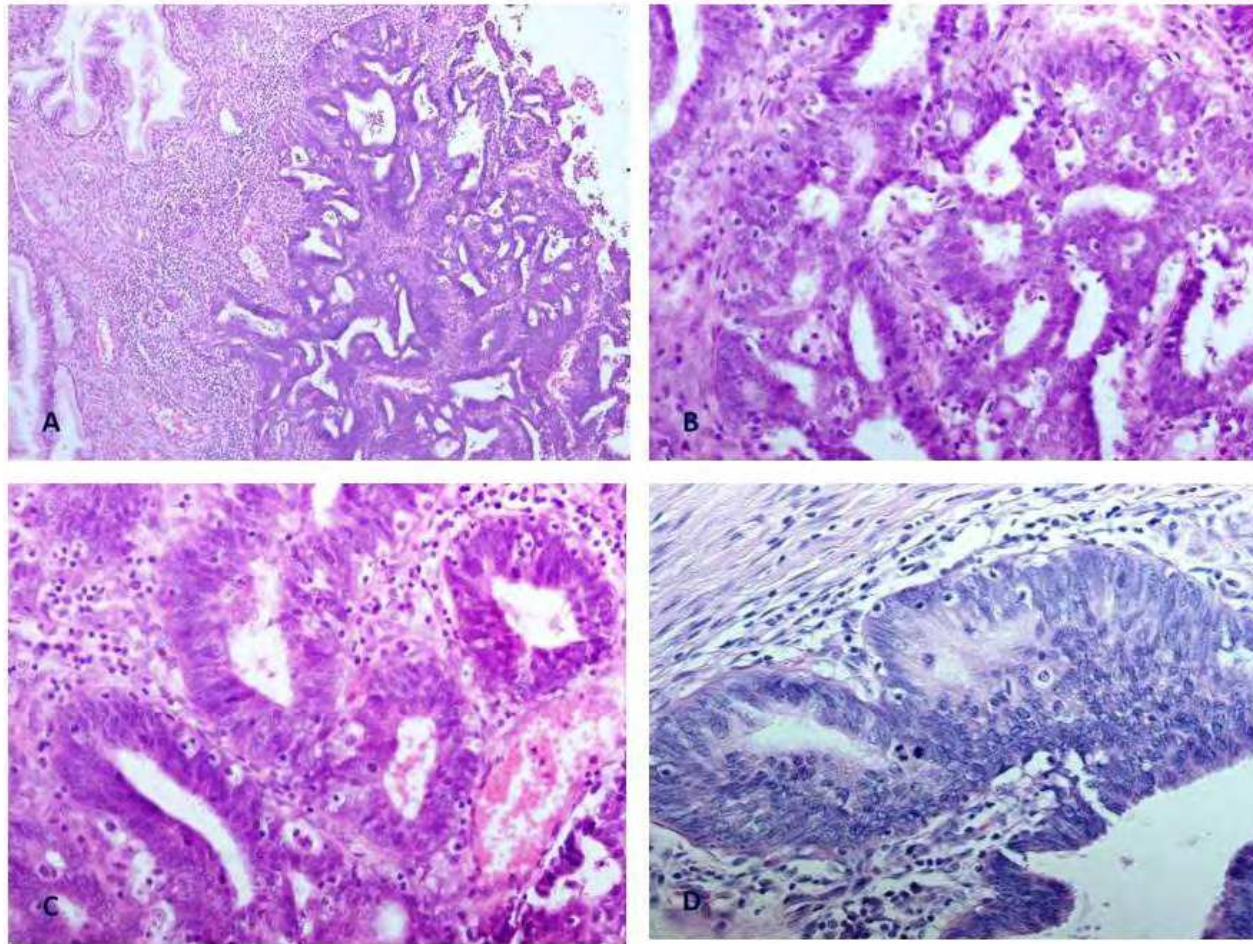
Fig. 4. HCGIN. **A,** Macroglands with secondary or multiple generation of bridging subdividing the lumen into smaller glandular spaces; no stroma supports the bridging cells (low power). **B,** Macroglands with secondary or multiple generation of bridging subdividing the lumen into smaller glandular spaces; no stroma support the bridging cells (High power). **C,** Nuclear stratification (loss of mucin secretion); nuclear hyperchromasia with mitotic activity and apoptotic bodies. **D,** Nuclear Stratification; loss of nuclear polarity with mitotic activity and apoptotic bodies.

2.5.2 Cervical cytology

The diagnostic category and the terminology of atypical glandular cell (AGC), has been widely used since it was first established at the 2001 Bethesda convention (Covell et al., 2003). Before 2001, AGC within The Bethesda System (TBS) were mentioned as atypical glandular cells of undetermined significance (AGUS). The incidence of endocervical adenocarcinoma has increased steadily over the past two decades (Hopkins & Morley, 1991). Since TBS was introduced, the diagnosis of AGC has risen and now accounts for 0.17–1.83% of all cervical smears (Nasu et al., 1993). The term AGC applies to glandular cells that demonstrate changes beyond those typical of benign reactive processes but lack sufficient features for a diagnosis of adenocarcinoma. Generally, the origin of AGCs, endocervical or endometrial, can be distinguished based on the larger nuclear size and more abundant cytoplasm of endocervical cells (Solomon et al., 1998).

Definition of architectural features
-Glandular crowding: A cluster of closely packed glands. **-Glandular budding:** Glands out-pouching into the surrounding stroma to produce "finger-in-glove" pattern. **-Glandular branching:** Glands with multiple out-pouching and irregular counters. **-Villoglandular /exophytic papillae:** Simple branching exophytic papillary pattern with thin delicate stromal stalk,reminds of villous adenoma of the GI tract. **-Intraluminal papillary projections:** Infolding of epithelium into the glandular lumina with supporting stroma which creates a cribriform-like pattern. **-Micropapillae pattern:** Intraluminal exuberance and delicate micropapillary projection with no supporting stroma. **-Cribriform pattern:** Macroglands with secondary or multiple generation of bridging subdividing the lumen into smaller glandular spaces; no stroma support the bridging cells.
Definition of cytological features
-Abrupt junction between the normal columnar epithelium and the CGIN: Partially affected epithelial lining by CGIN with sharp demarcation between normal epithelium and CGIN. **-Intestinal metaplasia /goblet cell formation:** A form of intestinal metaplasia, exhibits goblet cells and even paneth or neuroendocrine cells. **-Loss of mucin secretion in cells of endocervical type:** Reduction or complete absence of intracellular mucin. **-Nuclear stratification:** Pseudostratified up to stratified epithelium in reciprocal reduction in cytoplasmic mucin with or without loss of nuclear palisading and polarity. **-Nuclear changes:** Enlarged, elongated, pleomorphic and hyperchromatic nuclei with granular dense and evenly or abnormal dispersion of nuclear chromatin and presence of prominent nuclei. **-Mitotic activity**: Presence of juxtaluminal and increased numbers of mitotic figures (normal/or abnormal). **-Apoptosis (apoptotic bodies):** Markedly condensed homogenous nuclei (with or without nuclear fragmentation) often associated with densely eosinophilic cytoplasm.

Table 2. Definition of various architectural and cytological features of CGIN

The Bethesda System (TBS) recommends subclassification of AGC into the categories of *"favor endocervical origin"*, *"favor endometrial origin"* and *"not otherwise specified (NOS)"*. Favor endocervical origin lesions are further classified into the categories of *"favor neoplastic"* and *"favor NOS"* (Covell et al., 2003). However, subclassification of AGC has yet to be proved clinically effective, and although The Bethesda Committee and many others have studied cytologic criteria important in subclassification, these criteria have not been tested vigorously. The rates of AGC (reported as AGUS before 2001) quoted in the literature vary from 0.095% to 1.83% (Nasu et al., 1993; Mood et al. , 2006; Marques et al.,2011; Tam et al.,2003; Scheiden et al.,2004; Pecorelli et al., 2009).

According to TBS 2001, cytological features of subcategorized AGC is as follow:

In atypical endocervical cells (NOS) (Figure 5-A and B):

-      Cells occur in sheets and strips with some crowding and nuclear overlap.

- Nuclear enlargement, up to three to five times the area of normal endocervical nuclei, may be seen.
- Some variation in nuclear size and shape is present.
- Mild hyperchromasia is frequently evident.
- Nucleoli may be present.
- Mitotic figures are rare. Cytoplasm may be fairly abundant, but the nuclear /cytoplasmic (N/C) ratio is increased.
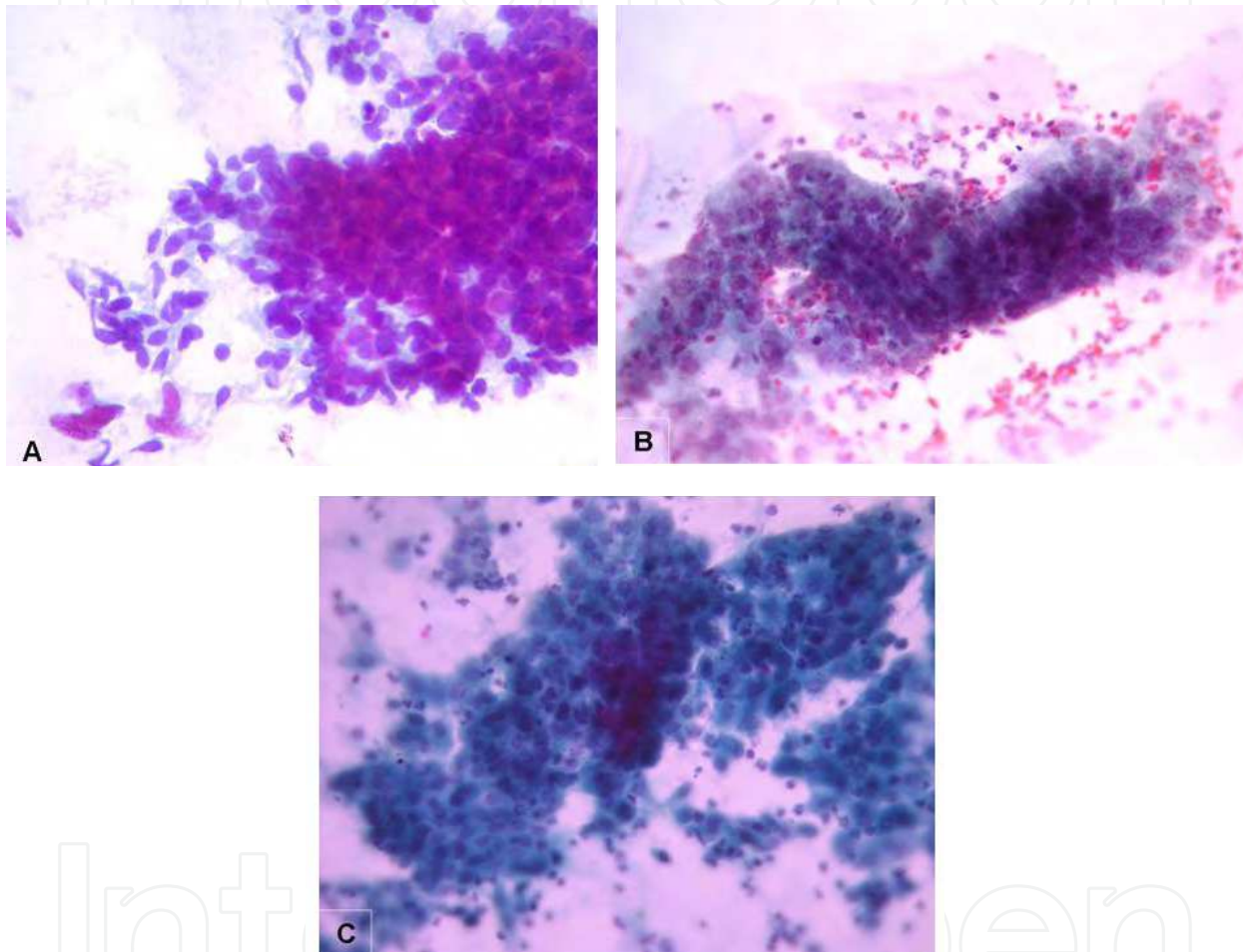- Distinct cell borders often are discernible.

Fig. 5. **A**, Atypical endocervical cells (NOS) .A sheet of endocervical cells with some crowding and nuclear overlap. **B**, Atypical endocervical cells (NOS). Strip of endocrvical cells with stratification, elongation of nuclei, nuclear enlargment and hyperchromasia . **C**, Atypical endocervical cells, (favor neoplastic). A sheet of endocervical cells with crowding and nuclear overlap shows increased nuclear/cytoplasmic ratios.The quantity of cytoplasm is diminished, and cell borders are ill defined.

In liquid-based preparation groups are more rounded and three dimensional with piled-up of cells, making individual cells in the center difficult to visualize.

In atypical endocervical cells, (favor neoplastic) (Figure 5-C) alongside above mentioned features, added cytological features incorporated:

- Cell morphology, either quantitatively or qualitatively, falls just short of an interpretation of endocervical adenicarcinoma in situ or invasive adenocarcinoma.
- Rare cell groups may show rosetting or feathering
- Nuclei are enlarged with some hyperchromasia
- Occasional mitosis may be seen.
- Nuclear/cytoplasmic ratios are increased, quantity of cytoplasm is diminished, and cell borders may be ill defined.

In liquid-based preparation groups may be three dimensional, thick, with layers of cells obscuring central nuclear detail.

It is important that the interpretation of "atypical glandular cells" (AGC) should be qualified, if possible, to indicate whether the cells are thought to be endocervical or endometrial origin. If the origin of the cells cannot be determined, the generic "glandular" term is used. Atypical endocervical cells should be further qualified when a particular entity, including neoplasia, is favored.

AIS is often identified in cytological specimens as abundant abnormal cells, typically with columnar configuration, single cells, two-dimensional sheets, or three-dimensional clusters and syncytial aggregates with nuclear crowding and overlap, without an accompanying tumor diathesis. Characteristic features of glandular differentiation include rosette formation, nuclear feathering ,and palisading (Figure 6-A and B).

In liquid-based preparation three-dimensional clusters are common. Chromatin is more open (vesicular) with irregular distribution and parachromatin clearing (Covell et al., 2003).
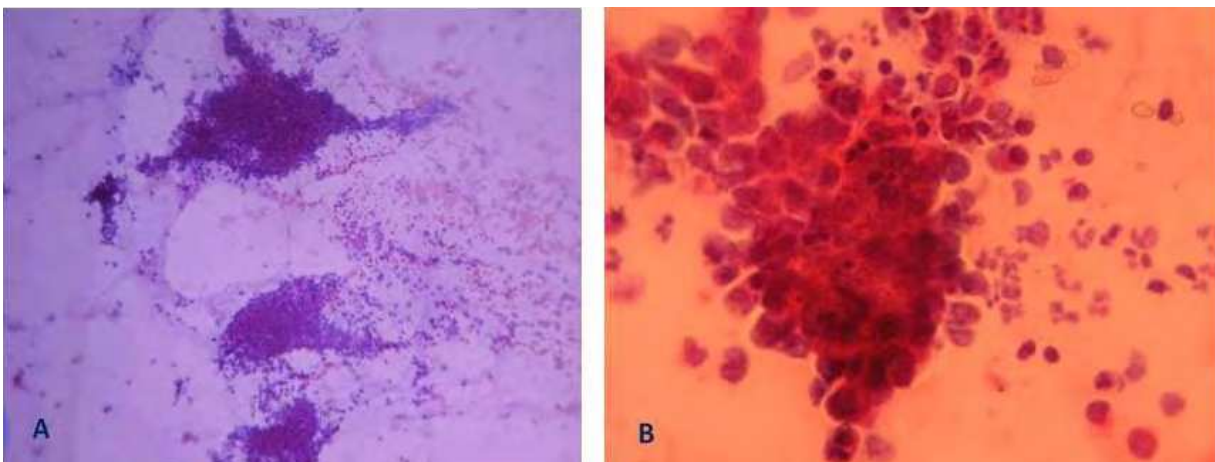

Fig. 6. Adenocarcinoma in situ. **A,** Abundant abnormal cells, typically with columnar configuration, single cells, two-dimensional sheets, or three-dimensional clusters and syncytial aggregates with nuclear crowding and overlap. **B,** Characteristic rosette formation in glandular differentiation.

2.5.3 Differential diagnosis

2.5.3.1 Invasive adenocarcinoma

The most important differential diagnosis of CGIN is microinvasive and invasive adenocarcinoma.

By definition the concept of microinvasive adenocarcinoma (MIA) is the same as microinvasive squamous cell carcinoma and represents an invasive adenocarcinoma with limited depth of stromal invasion up to 5 millimeters (Pecorelli et al., 2009). Despite plenty data about its squamous counterpart, MIA is suffering from a reliable cytological and histological diagnostic criteria as well as information about its prognosis and management. While diagnosis of early stromal invasion in squamous cell carcinoma (SCC) is relatively simple and easy, however, identifying early invasion in high grade CGIN may be extremely difficult or even impossible (McCluggage, 2000; Zaino, 2000; NHSCSP, 1999,Nucci,2002). High grade CGIN should be limited to the normal glandular field but problems occur when closely packed, architecturally abnormal glands are lined by dysplastic epithelium which fulfils the criteria for a diagnosis of high grade CGIN (McCluggage, 2000; Zaino, 2000; Nucci, 2002).

MIA characterized by effacement of normal glandular tissue by irregular atypical glands that extends beyond the deepest normal crypt associated with a stromal reactivity of desmoplastic, infiltration of chronic inflammatory cells or edematous type.

There are two certain features that identify the presence of invasion in endocervical adenocarcinoma (1) Individual cells or incomplete glands (Figure 7-A and B) lined by cytologically malignant-appearing cells at a stromal interface and (2) malignant appearing glands surrounded by a host response (Figure 7-C). It is important to determine that the glands are lined by cytologically malignant-appearing cells, because endocervicitis, microglandular hyperplasia, and ruptured mucin-filled glands all may have incomplete glands that at times may be associated with a host response of dense inflammation and, occasionally, edema or fibrosis. Unfortunately, many adenocarcinomas do not display these two changes yet are invasive. It should be noted that infiltration of chronic inflammatory cells around the CGIN may also be present and result in a confusing and complex status (McCluggage, 2000; Zaino, 2000; Nucci, 2002).

Additional features that are not entirely specific may help to identify invasion in other cases including:

(1) Architecturally complex, branching, or small glands, which grow confluently or in a labyrinthine pattern; (2) A cribriform growth pattern of malignant-appearing epithelium devoid of stroma within a single gland profile; (3) The presence of glands below the deep margin of normal glands; and (4) The presence of early stromal infiltration from glands involved by HCGIN of small buds of cells, often with a squamoid appearance (McCluggage, 2000; Zaino, 2000; Nucci, 2002).

Large masses of densely packed architecturally complex glands with luminal bridges and a cribriform growth pattern strongly suggest invasion. More difficult is the assessment of the "deep margin" of normal glands. Although it is stated that endocervical glands should be confined to the inner third of the cervix and less than 1 cm deep, benign glands in various patterns including nabothian cysts, tunnel clusters, laminar endocervical hyperplasia, deep endocervical glands, and mesonephric duct remnants may be found deeper in the stroma on occasion. Pathologists should, wherever possible, make every effort to make this distinction, but it is recognized that there will be cases in which the pathologist remains uncertain as to whether a lesion is invasive or not, even after the mandatory examination of many levels. This must be stated in the report (McCluggage, 2000, 2003; Zaino, 2000; NHSCSP, 1999; Nucci, 2002).
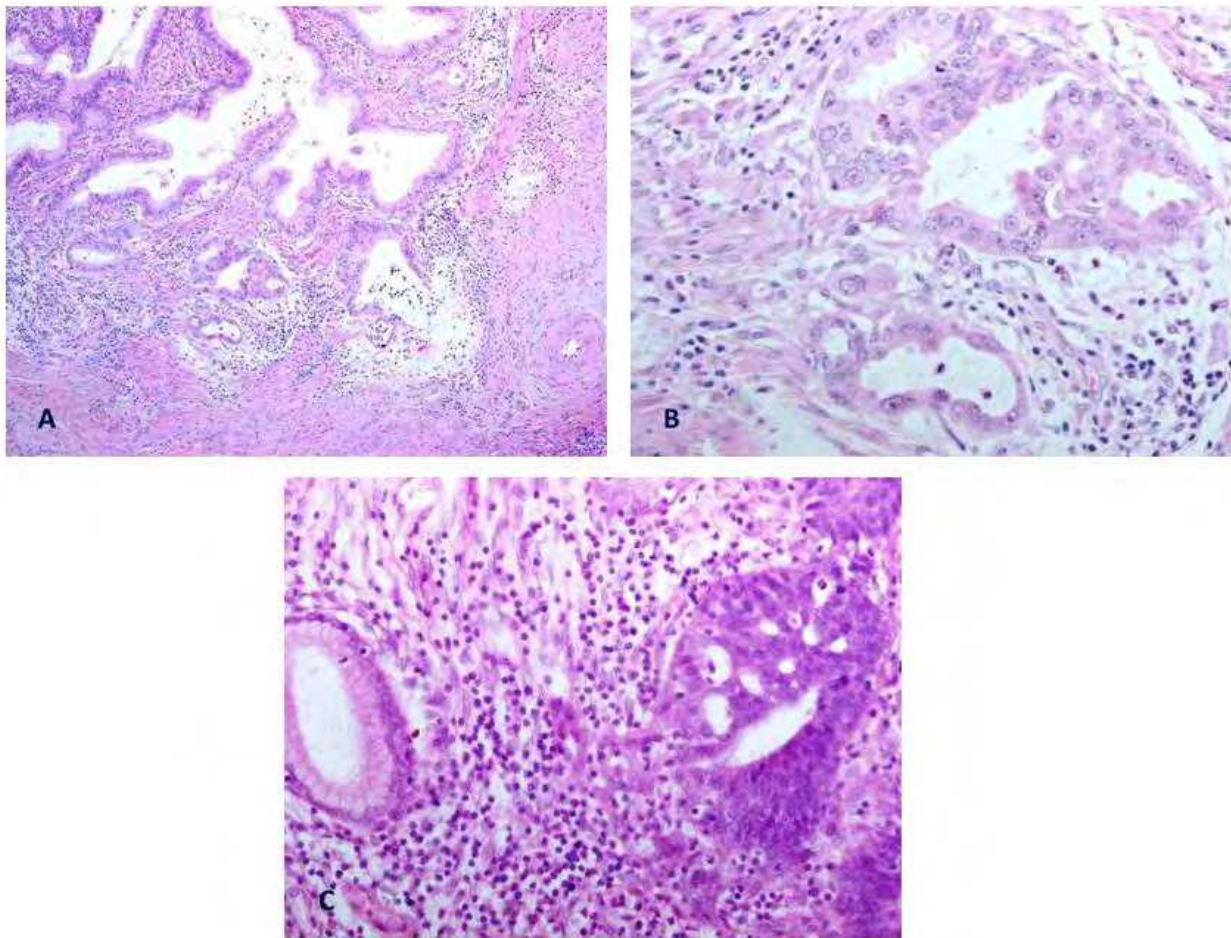
Fig. 7. Microinvasive adenocarcinoma. **A,** Individual cells and incomplete glands beneath the crypt surronded by edematous stroma and lymphocytic infiltration (low power). **B,** Individual cells and incomplete glands beneath the crypt surrounded by edematous stroma and lymphocytic infiltration (High power).Note the severe degree of cytological atypia. The nuclei are pleomorphic, there is loss of nuclear polarity and several nuclei contain large nucleoli. Cell above the incomplete gland has copious eosinophilic cytoplasm. **C,** A cribriform macrogland with cells in the lower right part with copious eosinophilic cytoplasm should arouse a suspicion that invasion may be present. Note normal gland in the left.

2.5.3.2 Tuboendometrioid metaplasia and Endometriosis

Tuboendometrioid metaplasia (TEM) is very common within the cervix and the most common lesion to be misdiagnosed as CGIN (McCluggage, 2000). It usually develops after cervical biopsy or diathermy, but may also occur in the absence of any surgical intervention. In TEM, the normal endocervical surface or crypt epithelium replaced by tubal or endometrioid cell type or by a population of cubo-columnar cells with regular, oval to round, darkly staining, hyperchromatic basal nuclei and high nuclear/cytoplasmic ratios; some of the cells may be ciliated (Figure 8- A and B). Tubal metaplsia usually involves a single gland or a few glands near the squamocolumnar junction and is not associated with inflammation.

Mitoses are uncommon except when estrogenic proliferative activity is present. Nuclear pleomorphism and atypical mitoses are absent (NHSCSP, 1999). A helpful clue to the diagnosis is the presence of cilia on the luminal border of some of the cells.

Occasionally invasive cervical adenocarcinoma may also contain ciliated cells, thus it is not need to overemphasize that the presence of cilia in the cervix does not unequivocally denote a benign process.

Ancillary techniques, such as the use of proliferation markers, have been used with some success in attempting to distinguish TEM and other benign glandular lesions from CGIN. These are discussed in detail later (McCluggage, 2000).

Endometriosis, which is characterized by the presence of endometrial-type glands set in an endometrial stroma, most commonly occurs in the region of the external cervical os or in the lower endocervical canal (Figure 9-A and B).

At colposcopy it appears as a hemorrhagic lesion. Regular bleeding may lead to stromal fibrosis and stenosis of the external cervical os. It can usually be easily recognized histologically and, if active, is most commonly approximately in phase with the intrauterine endometrium (NHSCSP, 1999) (Figure 9-C).

Cervical endometriosis not associated with TEM may have either a superficial or deep location. Deep cervical endometriosis is often associated with pelvic endometriosis and generally causes no problems in diagnosis. However, superficial endometriosis may be mistaken for CGIN (Tam et al., 2003). The presence of endometrial type stroma is a clue to the diagnosis but this is often significantly obscured by accompanying inflammation or hemorrhage and rarely by smooth muscle metaplasia. Particularly in young women there may be considerable mitotic activity when estrogen induced proliferative activity is present (McCluggage, 2000) (Figure 9-D).
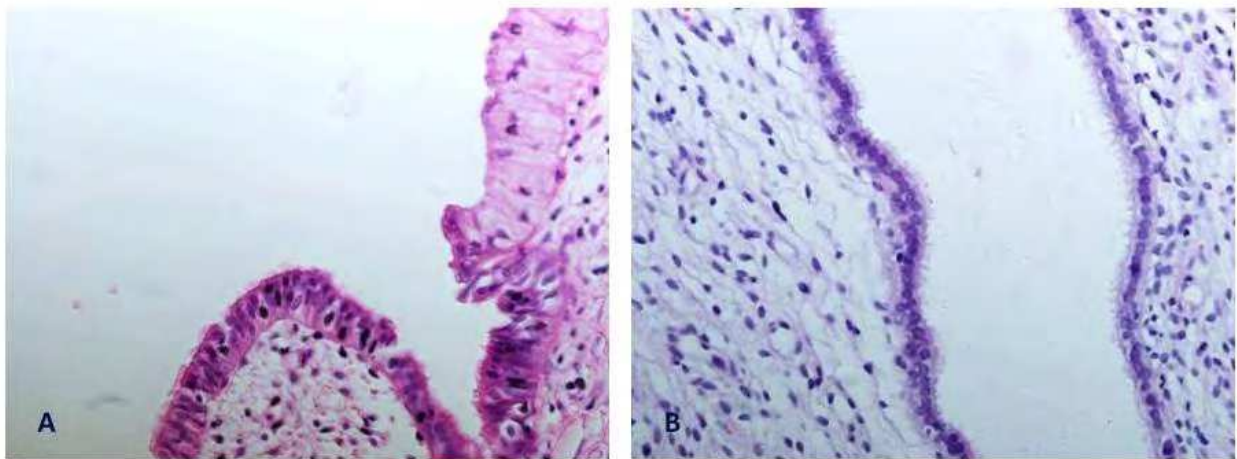

Fig. 8. **A,** Tubal metaplasia. Note abrupt transition between the mucus-secreting endocervical cells and the ciliated cells. **B,** Tuboendometrioid metaplasia (TEM). The normal endocervical crypt epithelium replaced by a population of cubo-columnar cells with regular, oval to round, darkly staining, hyperchromatic basal nuclei and high nuclear/cytoplasmic ratios; some of the cells may be ciliated.
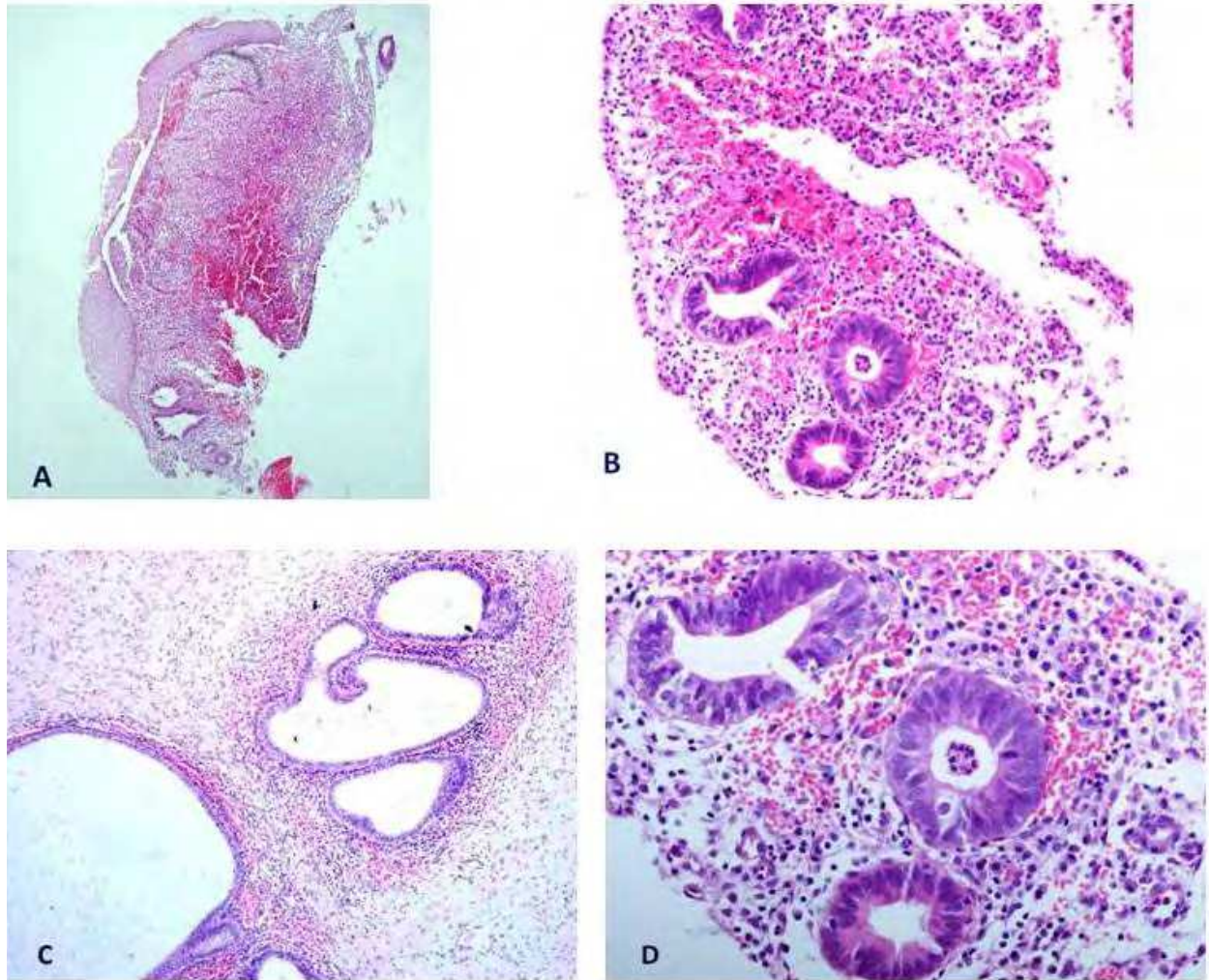
Fig. 9. Endometriosis. **A,** Presence of endometrial-type glands set in an endometrial stroma beneath the squamous epithelium (low power). **B,** High power view. **C,** Subnuclear vacuoles in active endometriosis. **D,** Note mitotic activity in estrogen induced proliferative activity.

2.5.3.3 Microglandular hyperplasia

Microglandular hyperplasia or microglandular adenosis is a common lesion, seems to be a result of progesterone effects, and most commonly found in pregnant women or those receiving oral contraceptives or progestines.

In gross findings is often polypoid and may be unifocal or multifocal (Fig. 10- A).

Early lesions may show sessile. Microscopically, it is characterized by the presence of closely packed small glandular structures lined by cuboidal epithelial cells with vesicular nuclei. Mitotic figures are uncommon, but may be found, and there is often prominent subnuclear and supranuclear vacuolation. There may be associated with reserve cell hyperplasia and immature squamous metaplasia and there is often a striking neutrophilic infiltrate (Figure 10- B and C).

Signet ring like cells may be seen. Typical or atypical forms of microglandular hyperplasia may be mistaken for CGIN or clear cell carcinoma. The suspicion of malignancy may be

heightened when microglandular hyperplasia results in a polypoid mass. CGIN and clear cell carcinoma generally have a higher mitotic rate than microglandular hyperplasia, atypical mitoses are often seen and nuclei are not vesicular (McCluggage, 2000; Zaino, 2000, 2002; NHSCSP, 1999; Ostör, 2000, Nucci, 2003).
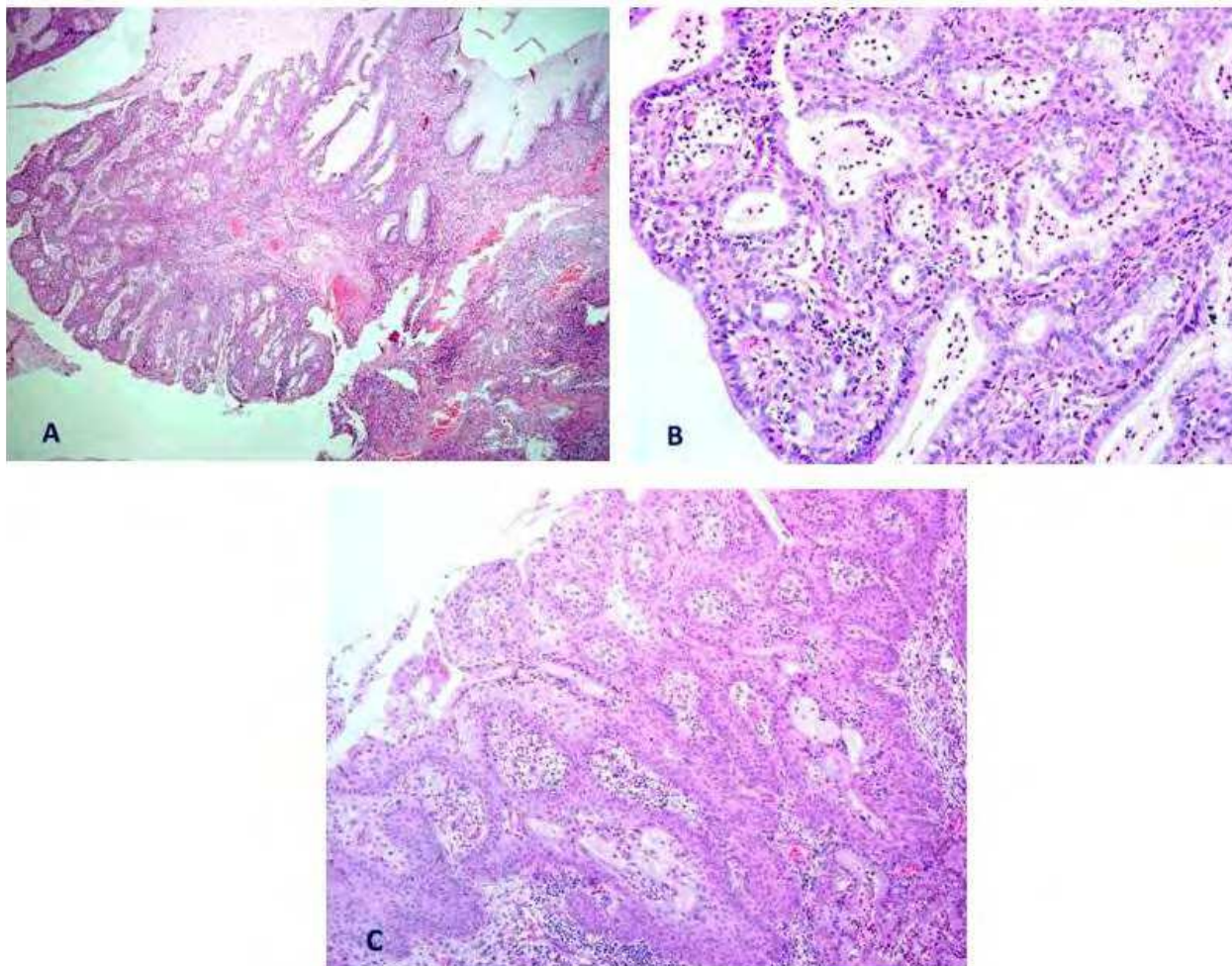

Fig. 10. Microglandular hyperplasia. **A,** Polypoid configuration (low power). **B,** Note small size glands and neutrophilic infiltration. **C,** Reserve cell hyperplasia and immature squamous metaplasia.

2.5.3.4 Tunnel clusters

Tunnel clusters are benign, relatively rare, endocervical lesions which are most common in multigravid patients. This has led some to suggest that they are a result of subinvolution of endocervical glands following pregnancy. Tunnel clusters are characterized by a lobular arrangement of closely packed, often dilated endocervical glands. The lining epithelium is of mucinous type but is often compressed and attenuated and filled by mucinous eosinophilic secretions. Nuclear pleomorphism and mitotic figures are absent and the lesion is always an incidental finding. Two histological types have been described. In type A there is little

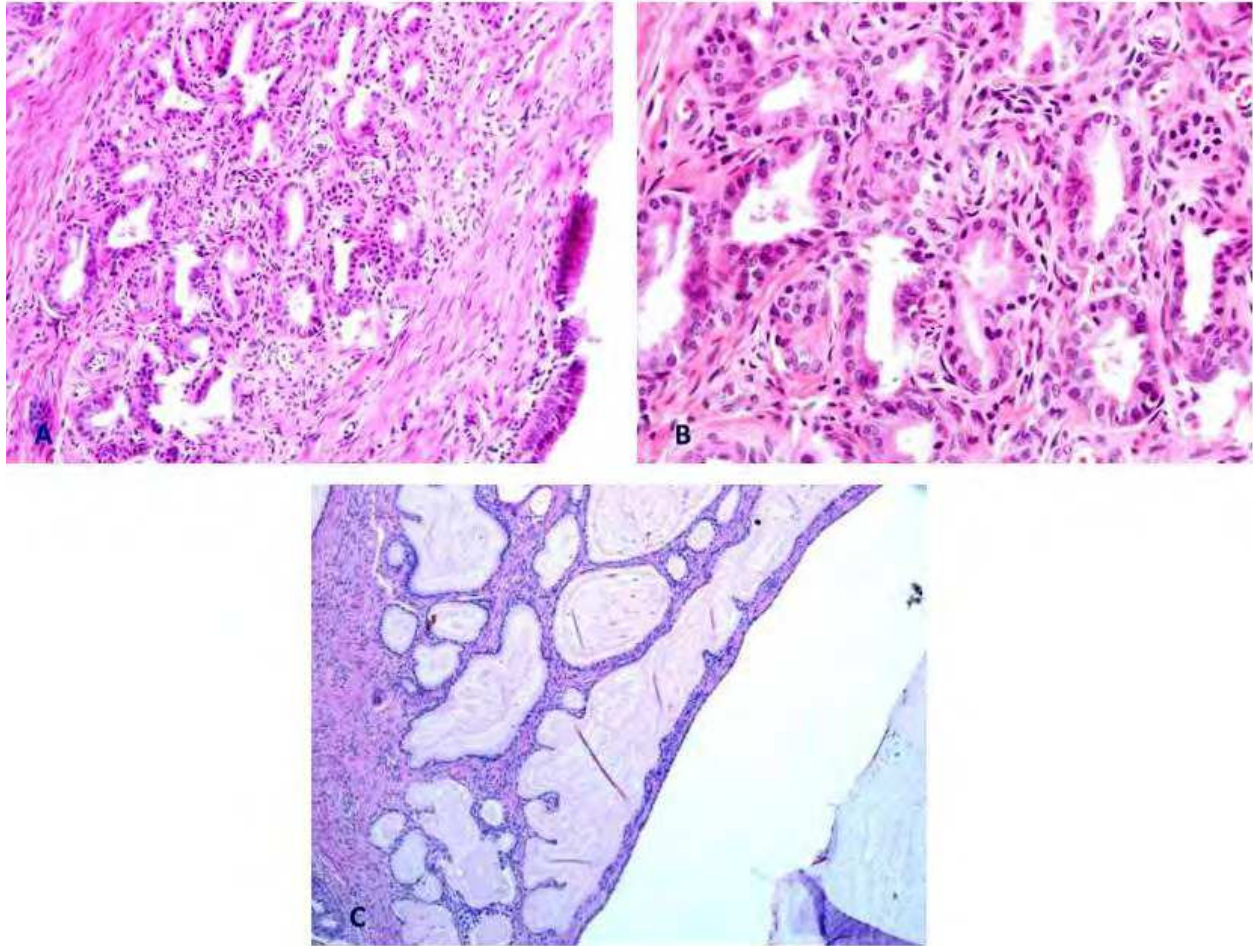or no dilatation of glands whereas type B is characterized by marked glandular dilatation (Figure 11).

Fig. 11. Tunnel clusters. **A,** Type A. Closely packed endocervical glands (Low power). **B,** Type A. (High power). **C**, Type B. Closely packed, dilated endocervical glands.

Although malignancy, especially minimal deviation adenocarcinoma (or adenoma malignum), may be considered, this is not a significant problem and once the characteristic histological features of tunnel clusters are known, they are easily appreciated (McCluggage, 2000; Zaino, 2000, 2002; NHSCSP, 1999; Ostör, 2000, Nucci, 2003).

2.5.3.5 Reactive glandular atypia

This very common category, including atypia as a result of inflammation, tissue repair, and response to irradiation, may mimic adenocarcinoma. Inflammation and tissue repair may result in lacelike masses of glandular cells with enlarged, pleomorphic nuclei and prominent nucleoli. Typically, the epithelium lining the glands is not stratified. The presence of a dense inflammatory infiltrate, frequently extending into the epithelium, often coupled with loss of polarity and acquisition of abundant, polygonal cytoplasm, assists in the recognition of the presence as reactive. Isolated multinucleated endocervical cells are common (Figure 12).
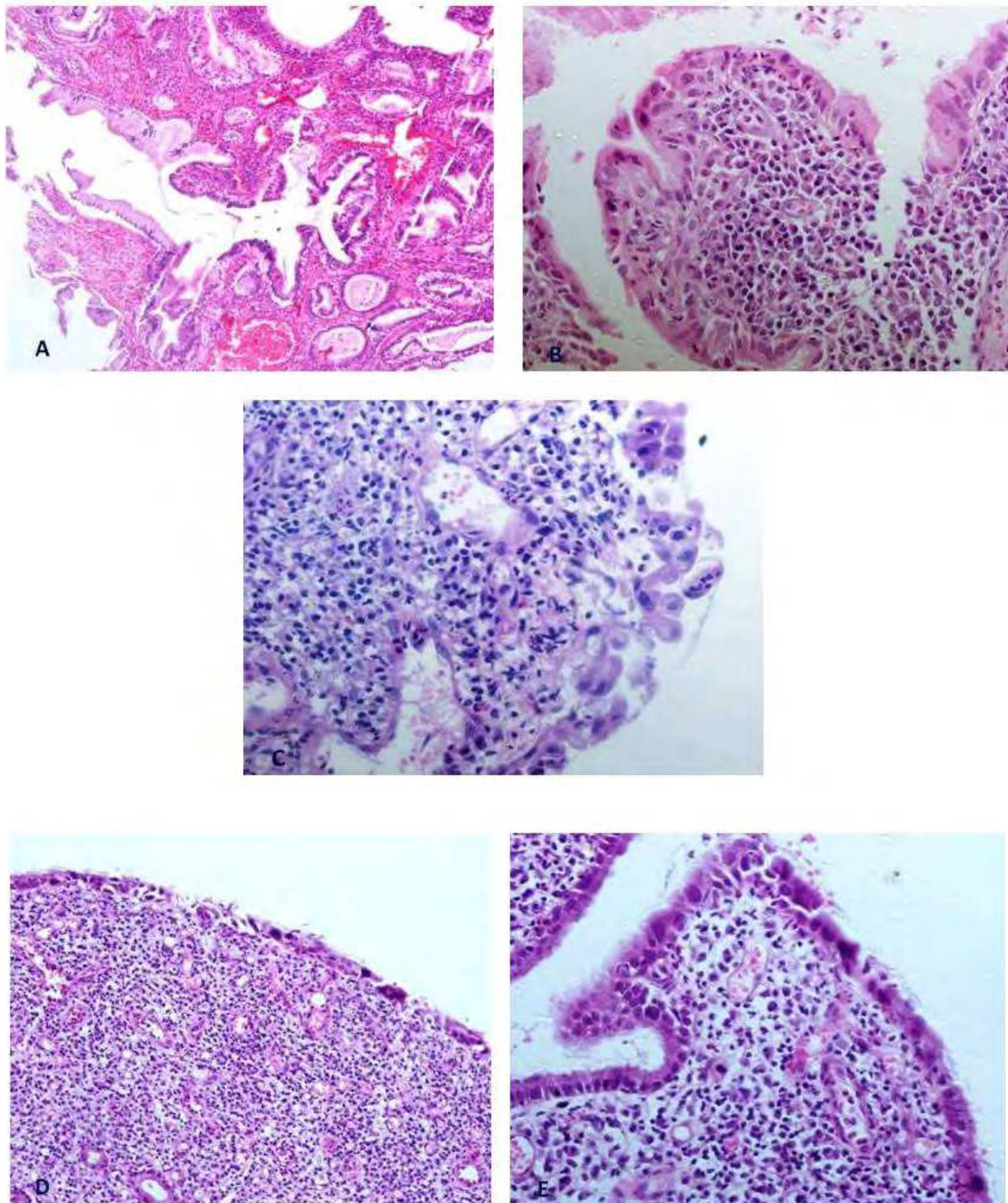
Fig. 12. Reactive glandular atypia. **A,** Note loss of polarity in a part of crypt lining produce abrupt transition and darker area between normal and reactive epithelium. **B,** Note enlarged, pleomorphic nuclei in endocervical epithelium. **C,** Dense inflammatory infiltrate, extending into the epithelium, coupled with loss of polarity.Enlarged, pleomorphic nuclei in endocervical epithelium and dense inflammatory infiltrate in the stroma. **D,** (Low power). **E,** (High power).

Reactive atypia is generally differentiate from CGIN by the lack of epithelial stratification, degenerative or reactive type changes in nuclear chromatin rather than granular hyperchromasia, and a paucity of mitotic activity and apoptotic bodies. Papillary endocervicitis is a specific form of tissue response characterized by relatively short edematous papillae, often containing lymphoid aggregates, covered by a simple columnar epithelium displaying nuclear changes of reactive cells. In contrast, radiation may result in glands being lined by large columnar or cuboidal cells with very large, hyperchromatic nuclei, but the chromatin is usually smudged and mitoses are rare. A clue to the reactive nature is that the abrupt transition to normal endocervix commonly seen in CGIN is not present (McCluggage, 2000; Zaino, 2000, 2002; NHSCSP, 1999).

2.5.3.6 Arias-Stella reaction

The Arias-Stella reaction is an incidental finding in about 10% of pregnant women. This reaction may involve endocervical glands as well as cervical endometriosis during pregnancy. The histological appearances of cells with enlarged pleomorphic nuclei and abundant vacuolated clear or eosinophilic cytoplasm are well known but may be misdiagnosed as CGIN or clear cell carcinoma. The fact that this lesion is focal and associated with the history of pregnancy facilitates the diagnosis. Mitotic figures are uncommon but may occur in the Arias-Stella reaction and indeed the presence of abnormal mitotic figures has been described in the Arias-Stella reaction involving endometrial glands (McCluggage, 2000; Zaino, 2000, 2002; NHSCSP, 1999).

2.5.3.7 Mesonephric remnants and hyperplasia

Mesonephric remnants take place in up to 22% of cervices. Their occurrence varies with the type of specimen because they are seldom seen in biopsy specimens, but are relatively common in conization and hysterectomy specimens in which deep portions of the cervix are routinely examined. The mesonephric or Wolffian ducts commonly persist as small remnants usually located in the lateral walls of the vagina or cervix, in the broad ligament, and in the hilus of the ovary. Microscopic lobules frequently surround a central duct within the deep cervical stroma. The acini are lined by cuboidal cells with oval, bland nuclei and scant to moderate quantities of eosinophilic cytoplasm. Mucin is not present in the cytoplasm, but a dense, periodic acid-Schiff (PAS)–positive, luminal secretory product is common. Hyperplasia typically is an incidental finding (McCluggage, 2000; Zaino, 2000, 2002; NHSCSP, 1999).

2.5.4 Ancillary techniques for distinction of pre-invasive lesions from benign mimics

Although the histological features of cervical glandular intraepithelial neoplasia are well described, but a wide variety of benign endocervical glandular lesions may be confused with CGIN and even invasive cervical adenocarcinoma. Many of these benign mimics are rare and in everyday practice the lesions most likely to be confused with CGIN are tuboendometrial metaplasia (TEM) and endometriosis. TEM is extremely common in the cervix, especially after loop or cone biopsy or some other operative procedure. The presence of cilia is a useful diagnostic clue to TEM, but these may be absent or inconspicuous, especially in cases showing endometrioid differentiation. Moreover, cervical TEM, especially when associated with a previous operative procedure, may have an altered stroma, raising the possibility of a desmoplastic reaction. Endometriosis within the

superficial cervix may also cause diagnostic problems, especially when the characteristic stroma is inconspicuous. Fibrosis, caused by previous episodes of hemorrhage, may result in consideration of a desmoplastic stromal reaction (McCluggage, 2003).

While tuboendometrial metaplasia and endometriosis are especially likely to be misdiagnosed as cervical glandular intraepithelial neoplasia, microglandular hyperplasia (MGH) is more likely to be mistaken for an invasive adenocarcinoma, usually clear cell adenocarcinoma. A diagnosis of low-grade CGIN (LCGIN) especially is poorly reproducible and, in many institutions, this diagnosis is rarely, if ever, made in the absence of high-grade cervical glandular intraepithelial neoplasia (Cameron et al., 2002).

Microglandular hyperplasia is also common within the cervix. Although most cases are easily recognized, atypical features may be found, including the presence of signet ring cells, stromal hyalinization, or a lace-like growth pattern. These features may cause confusion with invasive cervical adenocarcinoma, especially of the clear cell type (McCluggage, 2003).

Immunohistochemical staining using a panel of antibodies, namely- MIB1, bcl2, and p16 - may be extremely useful in problematic cases in distinguishing these benign mimics from high grade CGIN (HCGIN) or invasive adenocarcinoma; although it has been emphasized that careful morphological examination is the mainstay of diagnosis (Cameron et al., 2002). The proliferation marker MIB1, which reacts with the Ki-67 antigen, has been shown to be a useful adjunct to histology in distinguishing HCGIN from benign mimics. A proliferation index of > 30% is generally indicative of HCGIN, whereas most cases of TEM, endometriosis, and MGH exhibit a proliferation index of < 10%. However, there may be some overlap, with occasional cases of HCGIN also exhibiting a proliferation index of < 10%. In addition, in some studies occasional benign lesions have exhibited a proliferation index of up to 50% (Nucci, 2002; Ostör et al., 2000).

In general, however, there are great differences in the MIB1 index between TEM, endometriosis, and HCGIN. Characteristically, many positive nuclei are present in HCGIN, with only scattered immunoreactivity in benign lesions. Immunohistochemical staining for bcl2 may also be useful in distinguishing TEM and endometriosis from HCGIN. Some studies have shown that cervical TEM and endometriosis (but not MGH) show consistent cytoplasmic expression of bcl2 (Cameron et al., 2002; McCluggage, 2002, 1997). Most cases of CGIN are negative. Why cervical TEM and endometriosis should exhibit positive staining for bcl2 is not certain but interestingly there is strong positive staining of normal fallopian tube epithelial cells and of proliferative endometrium with antibodies to bcl2. Of course, TEM and endometriosis are morphologically similar to normal fallopian tube and normal proliferative endometrium, respectively.

Also CD10 is a useful marker for confirming the presence of endometrial stroma and in establishing a diagnosis of endometriosis; however, this is of limited value in the cervix since a rim of CD10 reactive stromal cells surrounds normal endocervical glands (McCluggage, 2003).

In the distinction of benign mimics from HCGIN, p16 staining may also be of value. Some studies have shown overexpression of p16 in high grade cervical squamous intraepithelial lesions and in low grade lesions associated with high risk Human Papilloma Virus (HPV) types, p16 overexpression seems to be related to the presence of high risk HPV types (McCluggage et al., 2003; Pavlakis et al.,2006; Li et al.,2007; Riethdorf et al.,2002). Cameron

et al. have founded a consistent positive staining of HCGIN (involving 100% of cells) with antibodies to p16. In contrast, cells of MGH were negative (Cameron et al., 2002). Staining of TEM and endometriosis was common but this was always focal and completely different to the pattern of immunoreactivity found in HCGIN. Thus, the combination of p16, MIB1, and bcl2 may be extremely useful in separating these benign mimics from HCGIN (McCluggage, 2003; Scheiden et al., 2004).

The diffuse distribution of p16 immunostaining in HPV 16/18 positive glandular neoplasms support a strong association with HPV infection and indicates that this biomarker mainly discriminate AIS from benign mimics (Riethdorf et al. , 2002). The situation with LCGIN has not been well studied and further work is necessary to ascertain whether these antibodies are of value in the separation of LCGIN from benign mimics. It is stressed that, in all cases, these antibodies are only of ancillary use and that careful morphological examination remains the cornerstone of diagnosis.

Immunohistochemical staining with carcinoembryonic antigen (CEA) has been reported to be of value in the separation of neoplastic endocervical glandular lesions and benign mimics (McCluggage, 2003). Diffuse cytoplasmic staining is usually present in neoplastic but not in benign lesions. However, as minimal deviation adenocarcinoma (MDA) is the neoplastic lesion most likely to be confused with benign lesions and as cytoplasmic staining with CEA may be focal and may not be present on a small biopsy, the value is limited. Conversely, normal endocervical epithelium may show luminal CEA positivity and some benign lesions, especially microglandular adenosis, may show cytoplasmic positivity, usually confined to areas of immature squamous metaplasia or reserve cell hyperplasia (McCluggage, 2003).

Other studies have found that a combination of CEA, MIB1, and p53 staining is useful in discriminating between benign and malignant endocervical glandular lesions (McCluggage, 2003; Pavlakis et al. , 2006). Polacarz et al. have shown *myc* immunostaining seemed to be a powerful discriminator between normal cervical glandular epithelium and epithelium show in intraepithelial changes or overt malignant changes. Apical cytoplasmic *myc* localisation thus seemed to be specific for CGIN and invasive adenocarcinoma of the cervix (Polacarz et al., 1991).

Other studies have evaluated the use of silver stained nucleolar organiser regions (AgNORs) in the separation of high grade CGIN and adenocarcinoma from benign histological mimics. In one study, significant differences in AgNOR counts were found between microglandular hyperplasia and HCGIN (McCluggage, 2000). However, the counting of AgNORs is laborious and time-consuming and is probably of less value than the use of proliferation markers.

In a recent study by Li et al.,their findings demonstrate significant expression of insulin-like growth factor-II mRNA-binding protein 3 (IMP3)and p16INK4a in adenocarcinoma in situ as compared to benign endocervical glands, suggesting that expression of these biomarkers may be helpful in the distinction of adenocarcinoma in situ from benign endocervical glands, particularly in difficult borderline cases (Li et al.,2007).

Findings of Little et al. study demonstrate that cyclin D1 can be included within an immunohistochemical panel to aid in the distinction between reactive cervical glandular lesions and adenocarcinoma in situ. The localized distribution of staining within invasive lesions suggests that cyclin D1 up-regulation has a specific role during the progression of some endocervical adenocarcinomas (Little & Stewart, 2010).

As result, immunohistochemical staining using a panel of antibodies may be very practical in problematic cases in distinguishing these benign mimics from high grade CGIN (HCGIN) or invasive adenocarcinoma; although it has been emphasized that careful morphological examination is the basis of diagnosis.

2.5.5 Approach to the diagnosis of cervical glandular intraepithelial neoplasia (CGIN) and pathological reporting

The approach to the diagnosis of CGIN is outlined below and is based on our experience and review of published article.

1. Generally speaking, the frequency of CGIN is low, and pathologists may rarely encounter to such a lesion in daily practice. Therefore in every case of cervical biopsy, it is rational to be aware of CGIN and its mimics and consider them in differential diagnosis.

2. Combination of invasive and pre-invasive lesions of squamous and glandular epithelium is a common event which has been reported in 30% to 70% of CGIN. Usually in low power examination, changes in a stratified squamous epithelium are more eye-catching and one may missed the concomitant glandular lesion. To prevent such a pitfall, we recommend to carefully examining the glandular epithelium architecturally and cytologically with low and high power field microscopy, especially when the lining of the canal and the glandular one had been replaced by a darker epithelium in each cervical specimen (Gloor & Ruzicka, 1982).

3. The next step is attention to any change in architectural pattern of endocervical glandular epithelium, including glandular branching, budding, crowding, infolding, villoglandular and cribriform, which is easily recognized even in low power microscopic examination. It is essential to emphasize that normal cleft and glands of endocervical epithelium can be variable in size and shape and may be mistaken for CGIN yet minimal deviation of adenocarcinoma. However comparison of the suspicious glands with uninquestionably benign ones in the vicinity may provide guidance and attention to the following points should help to exclude CGIN or carcinoma: absence of cytologic atypia, desmoplastic response and marked variation in size and shape of endocervical glands. However, regardless of presence, these criteria have not solved the difficulty in diagnosis, and this may require the examination of additional tissue (e.g. Cervical cone).

4. Even though some cytological features including stratification, mucin depletion and abrupt junction between normal and abnormal columnar epithelium, can be recognized in low power microscopic examination, emergence of a darker epithelium which indicate replacement of normal epithelium by stratified epithelium may be helpful.

5. As mentioned before, architectural pattern may be associated with benign conditions (cervicitis, tubal metaplasia, endometriosis, tunnel clusters and etc) or invasive adenocarcinoma and then must be combined with cytological features. The cytological features are nuclear changes, apoptotic bodies, mitotic figures and intestinal metaplasia can be evaluated exactly by x10, x 40 microscopic power examinations. Because many of cytological features may be associated with benign reactive changes or metaplastic condition; pathologist must be aware and combined cytological and architectural features for final diagnosis. High N/C ratio of the columnar epithelium in some metaplastic conditions can mimic endocervical or tubal type of AIS. Increased mitotic index (MI) especially atypical mitosis is a clue in the diagnosis of CGIN. The average MI of CGIN is intermediate between benign condition and invasive adenocarcinoma (Moritani et al.,

2002). Although mitosis is uncommon in benign condition, it is occasionally seen in endometriosis, estrogen consumption, and in the repair process (NHSCSP, 1999).

6. Apoptotic bodies are useful in establishing a diagnosis of CGIN, although they may not be prominent in all cases. Apoptotic body is a constant feature of HCGIN and the increase number of apoptotic bodies was significantly higher than in nonspecific endocervical glandular lesions (Moritani et al., 2002).

7. Most cases of CGIN are of usual endocervical type. However, other rare variants have been described. An endometrioid variant of CGIN has been reported. However, this is rare (if it occurs at all) and most cases diagnosed as such are probably cases of usual endocervical-type CGIN with scant intracytoplasmic mucin. An intestinal variant of HCGIN exists and is not uncommon. This is characterized by the presence of goblet cells and less commonly paneth or neuroendocrine cells (McCluggage, 2003). These microscopic features are along with Gloor study that was named CGIN type B alongside all other mentioned above features that described as CGIN type A (Pirog et al., 2000). It is doubtful whether intestinal differentiation in endocervical glands ever occurs without coexistent CGIN or invasive adenocarcinoma. Benign intestinal metaplasia involving endocervical glands has been described, but it is probably an extremely rare phenomenon, if it occurs at all, and the presence of goblet cells almost always indicates CGIN (Ioffe, 2003).

In regard to above mentioned approach the following points are emphasized in histological reporting of CGIN because these factors would influence the management:

1. Lesion location: exocervical, endocervical or both
2. Tridimensional lesion geometry: linear length of lesion and underlying crypt involvement depth. Clearly, there is no consensus in the acceptable depth of involvement. Ostor study revealed the depth of crypt involvement (measured from the surface) varied from 1.5 to 4 mm with an average of 2.6mm.The length of extent as measured horizontally in single section ranged from 0.5 to 30mm, with an average of 7mm.The width of the lesion (as determined from the number of blocks involved) ranged from 0.5 mm to 25 mm, with an average of 12 mm. From these parameters hypothetical tumor volumes could be calculated, the smallest being 0.25mm^3, and the largest 1,500 mm^3.The average tumor volume was 313 mm^3 (Ostör et al.,1984).
3. Potentional for AIS to be buried under metaplstic or dysplastic epithelium
4. Presence of squamous component (Colgan & Lickrish, 1990)
5. Possibly multifocal lesions and skip lesions
6. Possibly multicentric lesions (more than one quadrant involvement) or circumferential extent (Sheets, 2002)
7. Specimen margin status (post excision)

2.6 Biological behavior/management

It is beyond the scope of this chapter to discuss in detail the management of CGIN but it is clear that in those who wish to preserve their fertility (HCGIN and early invasive adenocarcinoma often occur in young women), local excision with careful pathological examination and free margins combined with close cytological follow up may be used for treatment. After completion of childbearing , hysterectomy is necessary because of the paucity of data concerning the long-term natural history of CGIN (Ostör, 2000; Sheets, 2002; Zhao et al., 2009).

3. Conclusion

There is a real increase in the incidence of malignant and premalignant endocervical glandular lesions, which are thus arrogant increasing importance in diagnostic surgical pathology but the frequency of CGIN is low, and pathologists may rarely encounter to such a lesion in daily practice. Therefore in every case of cervical biopsy, it is rational to be aware of CGIN and its mimics and consider them in differential diagnosis. In most, but not all, cases CGIN occurs close to the transformation zone and there is often an associated squamous intraepithelial lesion. CGIN can be confused with a wide variety of benign endocervical glandular lesions and even invasive cervical adenocarcinoma. CGIN should be classified as low grade or high grade CGIN. High grade CGIN is alternatively known as AIS and Low grade CGIN is alternatively known as glandular dysplasia. High grade CGIN is a vigorous diagnosis but distinction from early invasive adenocarcinoma may be difficult and Low grade CGIN may be underdiagnosed by pathologists. A combination of architectural and cytological features is necessary for diagnosis of CGIN. Immunohistochemical staining using a panel of antibodies may be useful in difficult cases in distinctive benign mimics from high grade CGIN or invasive carcinoma , although it is stressed that careful morphological examination is the basis of diagnosis.

4. Acknowledgment

5. Common abbreviations

AIS: Adenocarcinoma in situ
CGIN: Cervical glandular intraepithelial neoplasia
CIN: Cervical intraepithelial neoplasia
HCGIN: High grade CGIN
LCGIN: Low grade CGIN
MGH: Microglandular hyperplasia
MIA: Microinvasive adenocarcinoma
SCC: Squamous cell carcinoma
TBS: The Bethesda System
TEM: Tuboendometrioid metaplasia

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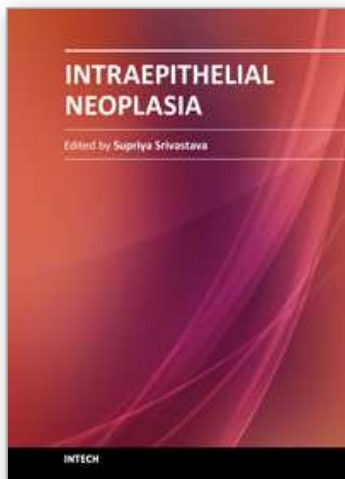
Intraepithelial Neoplasia

Edited by Dr. Supriya Srivastava

The book "Intraepithelial neoplasia" is till date the most comprehensive book dedicated entirely to preinvasive lesions of the human body. Created and published with an aim of helping clinicians to not only diagnose but also understand the etiopathogenesis of the precursor lesions, the book also attempts to identify its molecular and genetic mechanisms. All of the chapters contain a considerable amount of new information, with an updated bibliographical list as well as the latest WHO classification of intraepithelial lesions that has been included wherever needed. The text has been updated according to the latest technical advances.This book can be described as concise, informative, logical and useful at all levels discussing thoroughly the invaluable role of molecular diagnostics and genetic mechanisms of the intraepithelial lesions. To make the materials easily digestive, the book is illustrated with colorful images.

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