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REVIEW ARTICLE

Etienne Marbaix · Jean-Luc Brun

Concise survey of endometrial pathologies detected at hysteroscopy

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Abstract The paper briefly reviews the main pathologies of the endometrium that can be detected by hysteroscopy. Emphasis is put on dysfunctional endometrial bleeding and the recently discovered molecular mechanisms that trigger its occurrence, on the difference between hyperplasia and intra-epithelial neoplasia of the endometrium and on the DNA alterations commonly found in endometrial adenocarcinomas. This review of uterine pathology is intended for gynecologic endoscopists and is accordingly focused on lesions of the endometrium and of the inner portion of the myometrium.

Hysteroscopy and endometrial sampling

Hysteroscopy is usually performed to investigate either infertility or abnormal uterine bleeding. In the former condition, the uterine cavity will most often appear normal and no lesion, irregular development and/or ripening of the endometrium or an endometritis will be disclosed at histology. In abnormal bleeding, the uterus may contain endometrial hyperplasia, atrophy, neoplasia, polyp, adenomyosis, submucosal leiomyoma, uterine sarcoma or no lesion, leading then to the diagnosis of dysfunctional uterine bleeding [1].

Hysteroscopy is superior to dilation and curettage for evaluating abnormal uterine bleeding [2]. Indeed, the negative predictive value of hysteroscopy is >97% when no structural abnormality is disclosed in a completely visualized uterine cavity and when the endometrium appears uniformly thin and homogeneous [3, 4]. Theoretically, no further medical investigation should be necessary. However, because of the frequent lack of hysteroscopic diagnosis in case of endometritis, and considering the medico-legal climate that physicians currently face, systematic endometrial sampling may be recommended for pathological examination, even though the hysteroscopic view is negative.

Conversely, hysteroscopic detection of an abnormality is an indication for endometrial sampling. There is general agreement that a variety of endometrial sampling devices, including the Novak curette and pipelle biopsy, provide diagnostic accuracy equivalent to dilation and curettage [5]. However, all these blind methods may not be of interest in cases of focal intra-epithelial neoplastic lesion, uterine fibroids or endometrial polyp. Hysteroscopy with selected endometrial sampling allows the targeting of a focal lesion and improves the efficiency of the histological analysis. Endometrial polyps or focal hyperplastic endometrium should be excised entirely, as the positive predictive value for the diagnosis of structural intra-luminal pathology on the sole hysteroscopic view is only 40% [4]. This low value is probably due to gliding of the biopsy device on the surface of fibrotic lesions, and thus lack of adequate sampling of the lesion when a blind biopsy is performed after hysteroscopy. Hysteroscopic resection of the endometrium is generally not complete, but is at least equivalent to dilation and curettage regarding the extent of endometrial sampling. Histological analysis of shavings of the superficial myometrium and the overlying endometrium is adequate, although the tissue can be altered by the heating procedure at the edge of the shavings. Even adenomyosis may be suggested in the superficial myometrium despite the random orientation of the histological sections.

Dysfunctional uterine bleeding

Dysfunctional uterine bleeding is the main cause of metrorrhagia. It is defined as bleeding from the endometrium

E. Marbaix (✉)
Service d'anatomie pathologique,
Cliniques universitaires Saint-Luc,
Avenue Hippocrate 10, 1200 Bruxelles, Belgium
e-mail: marbaix@cell.ucl.ac.be
Tel.: +32-2-7641784
Fax: +32-2-7648924

J.-L. Brun
Department of Gynecology and Obstetrics,
Pellegrin University Hospital,
Place Amélie-Raba-Léon, 33076 Bordeaux, France

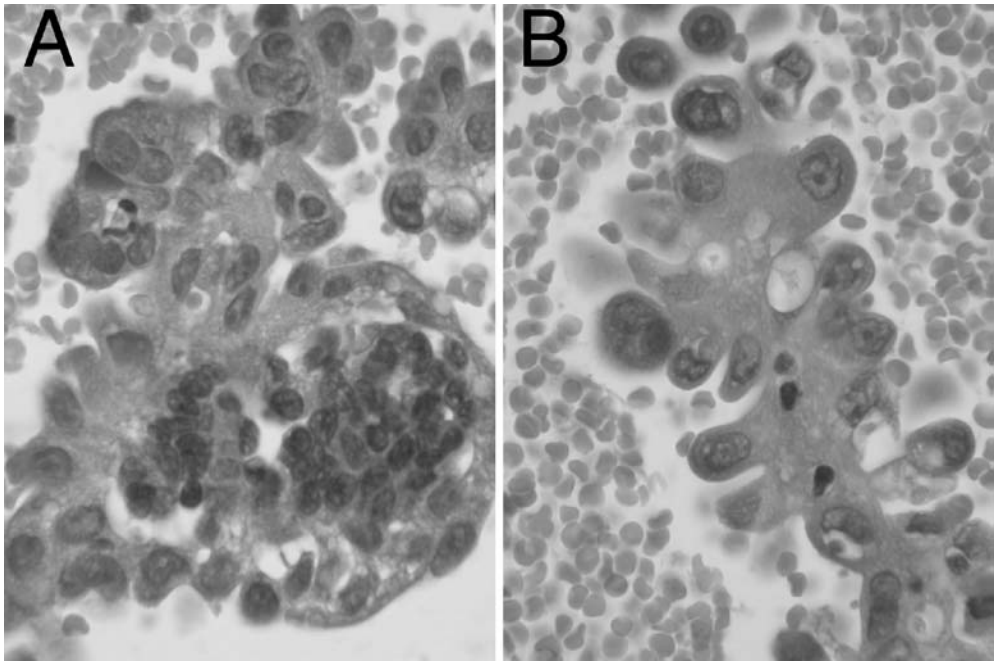

Fig. 1 Dysfunctional uterine bleeding. In *panel A*, a superficial endometrial fragment shed during an episode of dysfunctional bleeding in a 53-year-old woman shows the characteristic menstrual-like stromal breakdown. The overlying epithelium appears regenerative. *Panel B* illustrates a micropapillary tuft covered with regenerative epithelium showing worrisome features, such as large vesicular nuclei with prominent nucleolus

in the absence of pregnancy, of coagulation abnormality and of any pelvic lesion. Dysfunctional bleeding occurs either during hormonal treatment, in particular with progestins, or in its absence during spontaneous cycles as well as at menopause. It may occur upon prolonged estrogenic stimulation during anovulatory cycles and in hyperplasia, as well as in atrophic endometrium (see below). It is generally attributed to hormonal imbalance, but its relationship to sex steroids remains speculative at the present time [6].

When biopsied during bleeding, the endometrium consistently shows histological features of menstrual shedding, characterized by focal condensation of the stroma, tissue fragmentation and sloughing, and infiltration by neutrophils and other inflammatory cells (Fig. 1). At variance with menstruation, the glands will not display a late or exhausted secretory appearance, but will appear proliferative or atrophic according to the underlying hormonal condition. Shrinkage and fragmentation of the tissue is due to inappropriate and uncontrolled focal expression and activation of several matrix metalloproteinases (MMPs) and decreased expression of the tissue inhibitor of metalloproteinases-1 (TIMP-1) [7, 8, 9]. At menstruation, MMPs are similarly expressed and activated, but expression of TIMP-1 is increased. Thus, the decreased expression of TIMP-1 during the dysfunctional bleeding episodes further exacerbates the final activity of MMPs. MMPs degrade almost all constituents of the extracellular matrix [10] and are thus responsible for the menstrual-like stromal breakdown. As at menstruation, the surface epithelium regenerates to cover the denuded stroma and may produce syncytial papillary changes, in which epithelial cells form micropapillary tufts, are disordered and have a large nucleus with prominent nucleolus (Fig. 1). Most often bland, the cells may occasionally show worrisome regenerative atypias that should not be confused with intra-epithelial endometrial neoplasia (EIN, see below).

Usually, the biopsy is performed during non-bleeding intervals, and the tissue then appears either normal or with the expected histology for the underlying condition, i.e., proliferative or hyperplastic upon prolonged estrogenic stimulation, or atrophic upon hormonal treatment.

Endometritis

Endometritis may be missed on the sole hysteroscopic view if endometrial sampling is not performed [3]. Indeed, endometritis is a histological diagnosis based upon the demonstration of an abnormal pattern of inflammatory cell infiltrate (Fig. 2). Thus, acute endometritis is characterized by accumulation of neutrophils and eosinophils in the glands or beneath the surface epithelium in a non-menstrual endometrium, whereas chronic endometritis is diagnosed when plasma cells are present in addition to an increased number of normally present macrophages and lymphocytes, including the large granular lymphocytes, or granulocytes. Granulocytes are distinct natural killer cells that proliferate in the secretory endometrium and in the decidua. Retention of necrotic and fibrosed decidua fragments and placental villi is a common cause of endometritis. Rare specific forms of endometritis include tuberculosis, histiocytic endometritis and malakoplakia.

Adenomyosis

Hysteroscopy is of limited value to assess the presence of endometrial mucosa with dilated glands (crypts) inside the myometrium. The hyperplastic pattern of the endometrium

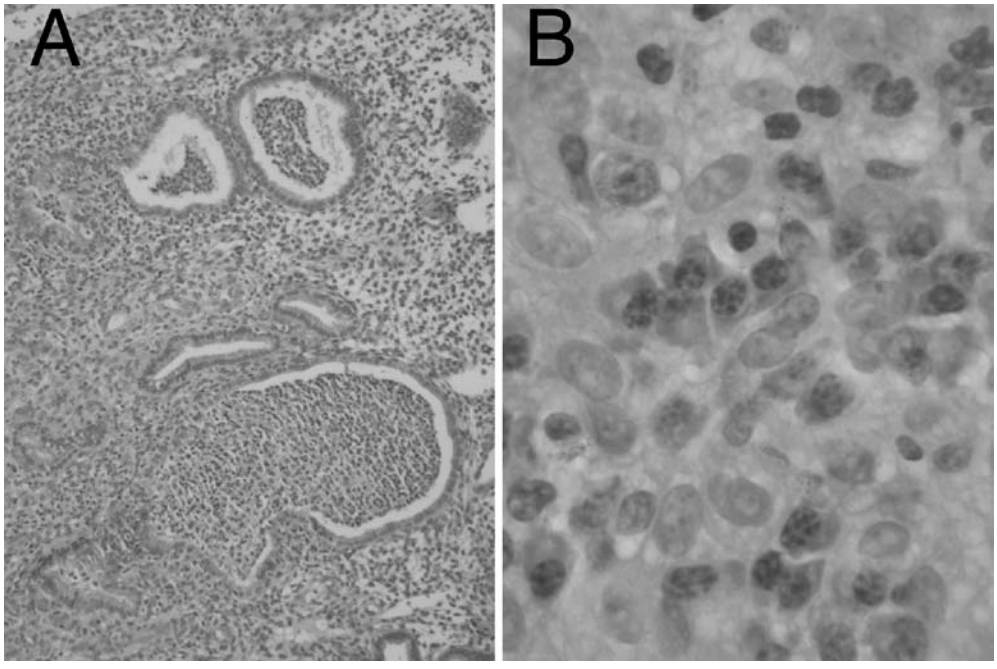

Fig. 2 Endometritis. Acute endometritis is shown in *panel A*. Neutrophils infiltrate the stroma, penetrate the epithelium and accumulate in glands, forming microabcesses. *Panel B* illustrates numerous plasma cells in the endometrial stroma, a hallmark of chronic endometritis

or its heterogeneous-appearing surface due to frequent concomitant interstitial myomas may be responsible for a high false-negative rate. In a regularly shaped uterus with endometrial atrophy, the crypts loaded with blood debris look like blue or brown spots, or small dips within the mucosa. The muscular hypertrophy appears as wild uterine inner sides, where the projection of bunches of muscular fibers are mixed with the endometrial crypts [11].

Histologically, adenomyosis is characterized by islands of endometrial glands and stroma inside the myometrium, together with hyperplasia of the surrounding myometrium in most cases. The intra-myometrial endometrial tissue is connected with the endometrium, its location resulting either from invagination of the mucosa inside the myometrium or from inclusion of the mucosa inside an "outgrowing" myometrium. The endometrial islands often look inactive like the basal layer of the endometrium, but may show secretory and menstrual features. The latter are responsible for prolonged and heavy menses. Because of its intra-myometrial location, adenomyosis cannot be sampled with a curette or a pipelle and can only be diagnosed on tissue shavings resected at hysteroscopy or on hysterectomy specimens.

Leiomyoma

Submucosal leiomyomas may cause bleeding by compressing and eroding the overlying endometrium. Hysteroscopy allows specification of the localization and the sessile (type 2) or pedunculated (types 0 and 1) implantation of the submucosal leiomyomas [11]. A biopsy with a curette or a pipelle will usually sample only the eroded and inflamed atrophic endometrium, but not the underlying smooth muscle neoplasm. The leiomyoma itself can be excised at hysteroscopy, or torn out when polypoid and protruding through the cervix. The leiomyoma is usually fibrosed, hence its common clinical designation as "fibroid." Areas of necrosis may occur, but they merge into fibrotic hyaline tissue and no atypia is found in the surrounding smooth muscle cells. In contrast, leiomyosarcoma shows a prominent mitotic activity, severe nuclear atypias, hemorrhages and clear-cut necrotic foci surrounded by non-fibrosed tumoral tissue.

Endometrial atrophy

Endometrial atrophy appears as a thin pallid or glossy mucosa. The vascular network of the superficial muscular layer may be visible through the thin endometrium. Endometrial sampling using the pipelle is often inefficient, but the sole hysteroscopic view is usually sufficient to establish the diagnosis. Bleeding episodes are associated with the occurrence of small superficial foci showing features of dysfunctional bleeding as explained above.

Endometrial hyperplasia

A hypertrophic mucosa with large hairy shreds is the prototypical hysteroscopic pattern of endometrial hyperplasia. Distinction between neoplastic transformation and benign hyperplasia requires endometrial sampling using a curette or selected endometrial resection in case of focal hyperplasia [12]. Actually, two different diseases were previously called endometrial hyperplasia: the non-atypical hyperplasia, which corresponds to a true hyperplasia and is the only lesion that can still be called hyperplasia, and the atypical hyperplasia, which is a precancerous le-

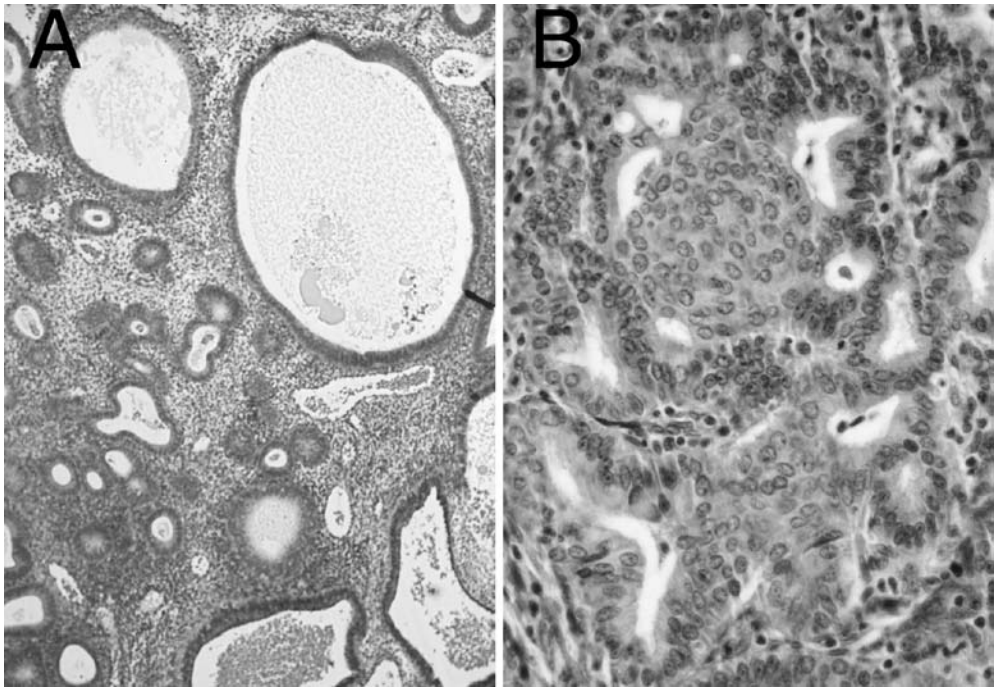

Fig. 3 Endometrial hyperplasia. *Panel A*: simple (glandulo-cystic) hyperplasia is characterized by a heterogeneous growth of the mucosa. The glands are irregularly developed, some being dilated, cystic, and others atrophic. *Panel B* illustrates a complex hyperplasia of the endometrium, with formation of morules inside the lumen of branching glands. Endometrial intra-epithelial neoplasia developed in this case of complex hyperplasia, as assessed by an exaggerated glandular crowding, loss of nuclear polarity and mild cellular atypias

sion and should rather be referred to as intraepithelial neoplasia (see below).

Endometrial hyperplasia results from continuous estrogenic stimulation of the endometrium as occurs during anovulatory cycles (polycystic ovary syndrome, premenopausal luteal deficiency) or after menopause, because of the conversion of ovarian and adrenal androgens into estradiol by the aromatase expressed in the peripheral fat tissue. Simple hyperplasia (or glandulo-cystic hyperplasia) is characterized histologically by an irregular and heterogeneous development of the mucosa, resulting in a variable thickening of the endometrium. The slow but continuous proliferation of the epithelial cells will induce a cystic dilation of some glands, alternating with other small glands, in a proportionally increased stroma (Fig. 3A). Epithelial cells are polarized as in a slowly proliferating endometrium and show no atypia. In complex hyperplasia (or adenomatous hyperplasia), cell proliferation is increased, resulting in gland budding and crowding of the epithelial cells. The resulting cellular aggregates, or morules, look like immature squamous metaplasia filling the lumen of the glands at the site of branching (Fig. 3B). Again, no cellular atypia should be observed.

During bleeding episodes, the tissue usually shows the histological pattern of dysfunctional uterine bleeding, with focal menstrual-like degradation of the stroma. Bleeding can also be secondary to ischaemic necrosis of a largely thickened mucosa, in particular when massive decidualization is induced by a progestogenic treatment. Endometrial hyperplasia will regress heterogeneously when the estrogenic stimulation fades with time. Thus, some areas of the endometrium will remain thicker than other places, and cysts will still be randomly present in a rather atrophic mucosa. The histological picture will gradually change into a senile cystic atrophy of the endometrium. One can easily understand the semantic dilemma generated by all the intermediate states between florid hyperplasia and complete cystic atrophy of the mucosa. Although not precancerous by itself, hyperplasia is associated with continuous cellular proliferation that increases the likelihood of DNA alterations, which can then lead to the transformation of the epithelial cells into a true neoplastic lesion and accounts for the increased rate of adenocarcinoma occurring in a hyperplastic endometrium.

Polyp

Functional endometrial polyps are usually small, with a wide and short pedicle, an irregular shape and a similar color to the adjacent endometrium during the follicular phase [11]. They may become transparent during the secretory phase. Non-functional polyps are classically larger, with a sharp pedicle, a rounded shape and a greyish color contrasting with the adjacent endometrium.

Histologically, an endometrial polyp is characterized by a fibro-vascular core covered by endometrial mucosa. In premenopausal women, the covering endometrium is functional and shows the proliferative or secretory differentiation similar to the surrounding normal endometrium. Because of incomplete shedding at each menstruation, it is progressively replaced by a basal-like mucosa, which shows poor secretory activity and slow proliferation. However, slow but continuous proliferation will lead to hyperplasia with cystic dilation of the glands (Fig. 4A). Thus, the endometrium covering the polyp will often be hyperplastic. Although a polyp by itself is not a precancerous lesion, its frequent association with hyperplasia

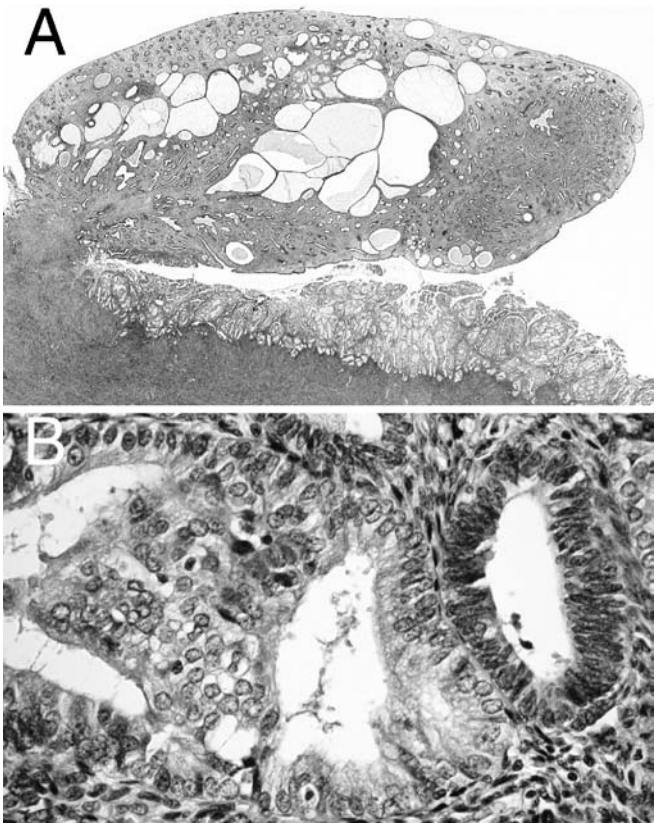

Fig. 4 Endometrial polyp and intra-epithelial neoplasia. The uterus of this 67-year-old woman treated for 10 years with conjugated estrogens displays a large polyp covered by a mucosa showing simple (glandulo-cystic) hyperplasia (*panel A*). An endometrial intra-epithelial neoplasia (*EIN*) developed in the surrounding mucosa, without any connection to the polyp. Compare the hypertrophic cells lining the neoplastic glands with the normal cells in the residual atrophic gland (*panel B*)

increases the risk of neoplastic transformation as in simple hyperplasia (see above). The curette or pipelle devices will not easily grasp the polyp at biopsy, and will often sample only the surface epithelium or the atrophic functional mucosa covering the fibrotic polyp core. Hysteroscopy with resection of the polyp is more appropriate to sample the polyp correctly.

Endometrial neoplasia

The classical hysteroscopic pattern of endometrial neoplasia is a heterogeneous hypertrophic endometrium with various foci of hypervascularization, vegetations or dips. Since the neoplastic process starts focally, diagnosis of endometrial intra-epithelial neoplasia (EIN) or adenocarcinoma obviously requires adequate endometrial sampling selected at hysteroscopy. The neoplastic focus may indeed be missed by a too limited or a blind sampling.

Precancerous lesion of the endometrium should be referred to as EIN instead of the previously used "atypical hyperplasia" [13]. The uncontrolled cellular proliferation results in an irregular budding and branching of the glands

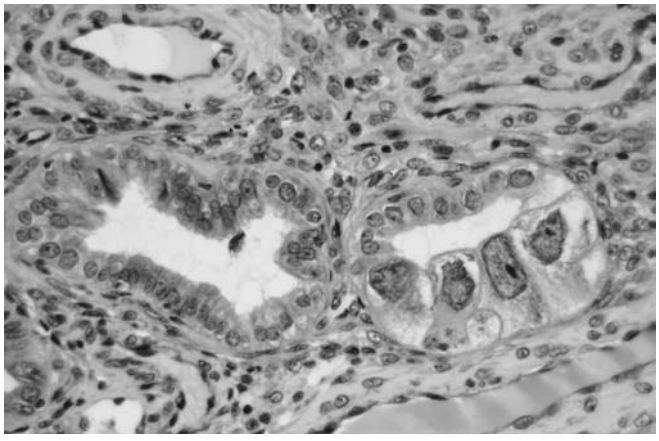

Fig. 5 Arias-Stella atypias. Huge, polyploid nuclei are found in some of the epithelial cells lining a small gland in an endometrium sampled 4 days post-partum

that will occupy more than approximately half the tissue area on histological sections (Fig. 4 A and B). Although occasionally conspicuous, the neoplastic changes often resemble the secretory differentiation of the epithelial cells and are difficult to identify. The cells are hypertrophic compared to the proliferating or resting epithelial cells of the normal mucosa and lose their polarity. There is an increased cytoplasmic content, which is lightly stained by eosin and gives a secretory appearance to the neoplastic cells. The nucleus is enlarged, round to oval, with a clear chromatin and a conspicuous nucleolus. However, the nucleus/cytoplasm ratio is often not increased and is even lower than in the normal resting or slowly proliferating epithelial cells, which show cytoplasmic atrophy. Conversely, foci of serous, secretory or mucinous metaplasia of the epithelial cells in an atrophic or hyperplastic endometrium may easily be misdiagnosed as intra-epithelial neoplasia if the lack of glandular proliferation and crowding is overlooked [14]. The Arias-Stella atypias induced by progesterone can be much more impressive than the neoplastic atypias (Fig. 5). Regenerative atypias of the surface epithelium as occurs at menstruation or during dysfunctional bleeding are also difficult to distinguish from neoplastic changes, in particular when the epithelium forms micropapillary tufts. Thus, mild cellular atypias should be interpreted with caution and always integrated with the histological appearance of uncontrolled glandular proliferation in order to diagnose EIN.

Adenocarcinoma occurs as soon as there is stromal infiltration by neoplastic glands. Irregular infiltration of glands in an altered fibroblastic stroma is the characteristic histological picture, but this feature is not easily recognized in biopsy samples because the stroma is often scanty and the myometrium absent. Thus, the following surrogates of stromal invasion are used as diagnostic criteria: (1) a confluent glandular pattern, which results either in a cribriform arrangement or confluent interconnected glands or (2) extensive papillary growth of epithelium and stroma into the glandular lumina. The en-

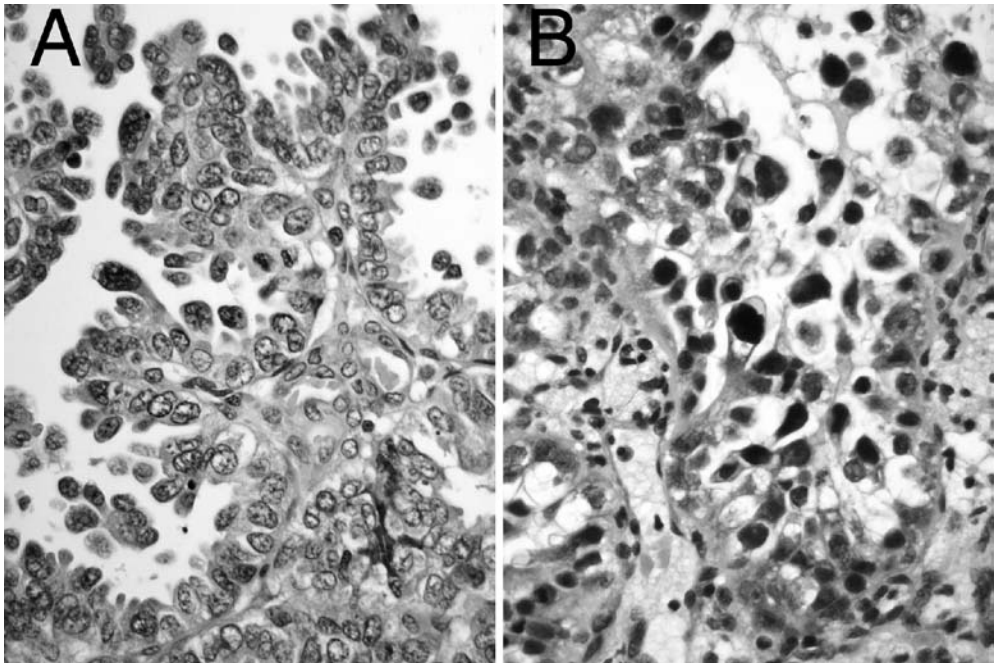

Fig. 6 Serous and clear cell adenocarcinomas of the endometrium. *Panel A* shows a serous adenocarcinoma of the endometrium. Branching papillae are lined by neoplastic cells showing severe atypias with marked nuclear polymorphism. *Panel B* illustrates a clear cell adenocarcinoma of the endometrium. The cytoplasm of many neoplastic cells appears optically empty. Nuclear atypias are prominent

dometrioid adenocarcinoma is the prototypical form of adenocarcinoma of the endometrium, in which neoplastic cells form endometrial-looking glands. Foci of squamous differentiation are found in a large number of endometrial adenocarcinomas, and adenoacanthoma was the previous term used for well-differentiated adenocarcinoma showing squamous differentiation. Squamous differentiation does not alter the prognosis of the carcinoma. In contrast, serous and clear cell adenocarcinomas are more aggressive variants of adenocarcinomas of the endometrium (Fig. 6). Serous adenocarcinoma frequently arises from a background of atrophy or polyp rather than hyperplasia, and is thus not related to a prolonged estrogenic stimulation of the endometrium. Histologically, it resembles papillary serous carcinoma of the ovary with delicate branching papillae covered by neoplastic cells showing high-grade atypias. Clear cell adenocarcinoma is characterized by neoplastic cells showing an optically clear cytoplasm or a hobnail appearance with nuclei protruding in the lumen of the neoplastic glands.

Carcinosarcoma (or malignant mixed Müllerian tumor) is an aggressive variant of poorly differentiated endometrial adenocarcinoma, showing partial transdifferentiation of the cancerous cells into homologous or heterologous sarcomatous components. These tumors usually present as bulging hemorrhagic and necrotic masses protruding inside the uterine cavity. Adenosarcoma also forms an exophytic mass, but usually lacks necrotic features. This rare neoplasm is a variant of the low-grade stromal sarcoma, developing inside the endometrium.

Since neoplasia is monoclonal, it starts from one cell and is thus focal in the endometrium. Obviously, the transforming mutations that lead to neoplasia will occur more frequently in a proliferating than in a resting tissue, and EIN thus develops more often from a hyperplastic endometrium than from an atrophic one. However, we all know cases of adenocarcinoma arising focally from an atrophic endometrium. The most frequent DNA alterations observed in EIN are: (1) methylation of the promoter of *hMLH-1*, silencing the gene that codes for a protein of DNA mismatch repair [15], (2) microsatellite instability, which results from deficient DNA mismatch repair, and (3) mutations or deletion of *PTEN* (Phosphatase and TENsin homologue), a tumor suppressor gene located on the chromosome region 10q23 that codes for a lipid phosphatase involved in a signal transduction pathway affecting cell survival [16]. Loss of chromosome 17p and mutation of p53 gene, often associated with an increased immunohistochemical labeling of the p53 protein, are observed in the aggressive serous variant of endometrial carcinoma [17].

In conclusion, although highly valuable and reliable as a method for the examination of the endometrium, hysteroscopy still needs to be completed by histological examination to obtain a definitive diagnosis when any abnormality is disclosed. It is to be hoped that visual targeting of the site of biopsy will further ameliorate the correlation between the macroscopic and the microscopic appearances of the various endometrial lesions enhancing the accuracy of the diagnosis and finally improving the care of the patient.

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