Pathophysiology of adenomyosis

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Adenomyosis refers to endometrial glands and stroma located haphazardly deep within the myometrium. Similar histological alterations may be found in extrauterine locations such as the rectovaginal septum. The aetiology and pathogenic mechanism(s) responsible for adenomyosis are poorly understood. Both human and experimental studies favour the theory of endomyometrial invagination of the endometrium, although the de-novo development of adenomyosis from Müllerian rests in an extrauterine location is a possibility. The prerequisite for adenomyosis may be triggered or facilitated by either a ‘weakness’ of the smooth muscle tissue or an increased intrauterine pressure or both. Relatively high oestrogen concentrations and impaired immune-related growth control in ectopic endometrium may be necessary for the maintenance of adenomyosis. Smooth muscle cell hyperplasia and hypertrophy are a reflection of reactive change secondary to ectopic endometrial proliferation. Further studies are needed for insight into the precise aetiology and pathogenesis of adenomyosis. Adenomyosis is a relatively frequent endomyometrial pathology discovered in multiparous women between 40 and 50 years of age. About 2/3 of women are symptomatic with menorrhagia and dysmenorrhoea; 80% of adenomyotic cases are associated with leiomyomata

Historical background and definition

It was Rokitansky (1860) who first alluded to the presence of endometrial glands in the myometrium as ‘cystosarcoma adenoides uterinum’. In 1896, Von Recklinghausen described the same phenomenon under the term ‘adenomyomata and cystadenomata of the uterus and tubal wall’. Cullen (1908) distinguished between adenomyoma, an intramyometrial tumour-like condition made of endometrial glands and stroma, and diffuse adenomyoma, in which both elements were distributed throughout the myometrium. The term ‘adenomyosis uteri’ was first used by Frankl (1925). In 1972, Bird et al. defined adenomyosis as ‘the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium’. This definition still prevails today; however, we like to qualify it further as to the presence of endometrial glands and stroma located haphazardly and deep within the myometrium. The issue of depth is important because the normal endomyometrial junction is often irregular, and adenomyosis must be distinguished from minimally invaginated basalis surrounded by myometrium (Figure 1). There are two ways to circumvent this problem. The first is to determine whether there is myometrial hypertrophy (‘collar’) around foci of adenomyosis. Such alteration is not seen at the endomyometrial junction (Figure 2). The second is to measure the distance between the endomyometrial junction and the closest ade-
nomyotic foci. This should be ~25% of the total thickness of the myometrium. The latter approach is particularly relevant in the postmenopausal and gravid uterus because periadenomyotic muscular hypertrophy in these uteri is generally absent (Hendrickson and Kempson, 1980). Although many consider adenomyosis a variant of endometriosis, so-called internal endometriosis (Emge, 1956; Israel and Woutersz, 1959), we like to define endometriosis as endometrial glands and stroma located outside of the myometrium, e.g. uterine serosa, posterior subperitoneal surface of the corpus, etc.

Pathogenesis

The precise aetiology and the developmental events leading to adenomyosis are unknown. A number of theories have been proposed in the past 50 years and these have been reviewed in detail by Ridley (1968). Currently, the most widely held opinion is that adenomyosis develops as a result of down-growth and invagination of the basalis endometrium into the myometrium. Indeed, one can often see direct continuity between the basalis endometrium and the underlying adenomyosis in the myometrium. In extrauterine regions such as the rectovaginal septum, adenomyosis may develop de novo from embryologically misplaced Müllerian remains.

The triggering mechanism of endometrial ‘invasion’ of the myometrium in humans remains to be determined. Proliferative changes such as mitotic activity, increased nuclear DNA synthesis and ciliogenesis are significantly more pronounced in the functionalis than the basalis layer of the endometrium (Ferenczy and Bergeron, 1991). The biological rationale for the geographic variation in proliferative indices may lie in the difference in physiological functions of the functionalis compared to the basalis layer. The former is the seat of blastocyst implantation, whereas the latter provides the origin for the regenerative endometrium following menstrual degeneration of the functionalis (Ferenczy, 1980). During periods of regeneration, epithelial cells from the stump of basalis glands are in direct contact with the spindle-shaped cells of the endometrial stroma, and ultrastructurally contain intracellular filamentous/trabecular systems and pseudopodial cytoplasmic projections. These features are consistent with migration by amoeboid contraction and expansion (Ferenczy, 1980). Such morphological alterations have as yet not been described in adenomyotic endometrial glandular epithelium. Nevertheless, in-vitro studies showed that endometriotic cells have invasive potential and their invasion index is similar to that of metastatic bladder cell lines.
(Gaetje et al., 1995). Such invasive potential may facilitate extension of the basalis endometrium into the myometrium. In MCF-7 breast cancer cells, production of tenascin is stimulated by the hormonally regulated epidermal growth factors (EGF) (Chiquet-Ehrismann et al., 1989). The fact that endometrial stromal fibroblasts produce tenascin, a fibronectin inhibitor which in turn facilitates epithelial migration suggests a complex physico-chemical interrelationship during the process of endometrial growth processes. Tenascin has been immunolocalized around proliferative phase endometrial glands but not in post-ovulatory phase endometrial glands (Vollmer et al., 1990). It is possible that tenascin mediates epithelial–mesenchymal interactions by inhibiting cell attachment to fibronectin in adenomyotic type endometrium as it does in its endometrial counterpart.

A recent study using in-situ hybridization and immunohistochemistry demonstrated that endometrial glands in adenomyosis selectively express more human chorionic gonadotrophin (HCG)/luteinizing hormone (LH) receptor mRNA and immunoreactive receptor protein than the non-invaginating glandular epithelium (Lei et al., 1993). In normal endometrium, the glands fail to demonstrate geographic variation (as a function of their depth) in HCG/LH receptor expression. It is thus possible although not proven that the increased receptor expression of invaginating endometrial epithelium may be related to the potential to invaginate into the myometrium and form adenomyotic foci. It is of interest that increased HCG/LH receptor expression was found in endometrial carcinomas compared to non-invaginating trophoblasts in choriocarcinomas (Lin et al., 1994).

Earlier steroid receptor studies using cytosol preparations yielded inconsistent results; some found no progesterone receptors in 40% of the adenomyotic cases studied (Tamaya et al., 1979), whereas others found higher progesterone than oestrogen receptor concentrations (van der Walt et al., 1986). Using immunohistochemical tracing techniques the author found relatively high concentrations of both oestrogen and progesterone receptors in both the basalis and adenomyotic endometrium (unpublished observations) (Table I). Oestrogen receptors are prerequisites for oestrogen-mediated endometrial growth. Although there is no clear-cut evidence of impaired hormonal environment in most women with adenomyosis, hyperoestrogenaemia may play a role in the invagination process since high frequency of endometrial hyperplasia is found in women with adenomyosis. According to some researchers, a relatively high oestrogen concentration is necessary for the development and maintenance of adenomyosis as well as endometriosis (Yamamoto et al., 1993). Supporting this contention is the clinical observation that suppression of oestrogenic environment by danazol induces involution of the ectopic endometrium as well as the associated symptoms such as menorrhagia and dysmenorrhoea (Yamamoto et al., 1993). Akin to uterine leiomyomata, oestrogen is synthesized and secreted in adenomyotic tissues (Yamamoto et al., 1993). These investigators demonstrated both aromatase and oestrogen sulphatase activities by steroidochemical analysis in the supernatant fraction of myometrium containing foci of adenomyosis. Oestrogen sulphatase and particularly aromatase activity was higher than that observed in the normal adjacent myometrium, leiomyomata and overlying endometrium ($P < 0.01–0.001$). Moreover, endometrial enzymatic activity was suppressed in vitro by up to 50% after addition of $10^6$ M danazol (Yamamoto et al., 1993). Aromatase was also demonstrated by immunohistochemistry in the cytoplasmic substance of gland lining cells but not stromal cells in foci of adenomyosis in human uteri.

### Table I. Immunohistochemical characteristics of uterine adenomyosis, endometriosis, basalis endometrium and leiomyoma

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Adenomyosis</th>
<th>Endometriosis</th>
<th>Basalis endometrium</th>
<th>Leiomyoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diffuse</td>
<td>Focal (adenomyoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>S</td>
<td>M</td>
<td>G</td>
</tr>
<tr>
<td>AE1/AE3</td>
<td>4+</td>
<td>-</td>
<td>1+</td>
<td>2+</td>
</tr>
<tr>
<td>Vimentin</td>
<td>1+</td>
<td>1+</td>
<td>-</td>
<td>1+</td>
</tr>
<tr>
<td>ER</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
<td>2+</td>
</tr>
<tr>
<td>PR</td>
<td>3+</td>
<td>4+</td>
<td>4+</td>
<td>3+</td>
</tr>
<tr>
<td>Actin</td>
<td>-</td>
<td>-</td>
<td>3+</td>
<td>-</td>
</tr>
<tr>
<td>Desmin</td>
<td>-</td>
<td>-</td>
<td>3+</td>
<td>-</td>
</tr>
</tbody>
</table>

AE1/AE3 = low and high molecular weight cytokeratin; ER/PR = oestrogen/progesterone receptor; G = glandular epithelium; S = stromal cells; M = myometrium surrounding ectopic endometrium; SE = surface epithelium.
Oestrogen production by adenomyotic tissue is also supported by finding more women with high oestradiol concentration (≥30 pg/ml) in the menstrual blood in those with adenomyosis than in those without adenomyosis and normal ovulatory cycles (Takahashi et al., 1989). The secretory response of adenomyotic tissue to hormonal stimulation is consistent with effective progestogenic influence on the ectopic endometrium. Progestogens enhance aromatase activity both in eutopic and adenomyotic tissues (Urabe et al., 1989) contributing thereby to oestrogen biosynthesis in adenomyotic foci.

It may be that bioavailability of sex steroids is not sufficient alone to produce adenomyosis. It is possible that the myometrium in cases of adenomyosis is either predisposed to be invaded by the basalis endometrium, and that ‘benign invasion’ of the endometrium occurs secondary to ‘weakness’ of the myometrium, or that myometrial weakness is caused by trauma, such as curettage, myomectomy and Caesarean section. In this regard, adenomyosis can be produced in pregnant rabbits by curetting one horn and tube, while retaining pregnancy in the opposite horn (Lewinski, 1931). It is possible, although not proven, that myometrial invasion by the endometrial basalis is enhanced by increased intrauterine pressure which, according to Cullen (1908), could be produced by elevated concentrations of circulating progesterone.

Increased expression of the major histocompatibility complex class II antigen (HLA-DR) in the gland cells of normal (eutopic) and ectopic endometrium (18 patients) and adenomyosis (50 patients) was observed by immunohistochemistry (Ota and Igarashi, 1993). In addition, macrophages in the myometrium of adenomyosis appear to be increased; these may activate helper T cells and B cells to produce antibodies. Autoantibodies against phospholipids in endometriosis and adenomyosis as well as marked deposition of immunoglobulin (Ig)S or complement components have been observed (Weed and Arquembourg, 1980; Kreiner et al., 1986). The precise significance of these aberrant immune phenomena in adenomyosis or endometriosis is not understood at present.

Experiments in vitro showed that activated CD3+ T cells in the endometrium and their secretory product interferon-γ induce expression of HLA-DR immunoreactivity in endometrial gland cells and inhibition of their proliferation (Tabibzadeh et al., 1993). The closer the endometrial cells are to activated T cells, the greater is their growth-inhibition. It appears that lymphoid follicle-like structures, mostly located in the endomyometrial junction, are rich in activated T helper cells. Their location coincides with maximal inhibition of endometrial growth observed both morphologically (Ferenczy et al., 1979) and by proliferation marker studies (Tabibzadeh et al., 1993). Conversely, endometrial proliferation is at its maximum near the endometrial surface far away from basalis-containing lymphoid aggregates (Ferenczy et al., 1979; Tabibzadeh et al., 1993). It is plausible, although not proven, that adenomyotic uteri are poor in activated T cells, thus the basalis endometrium may have growth advantage over non-adenomyotic, lymphoid-rich basalis endometria. Whether such anomaly is necessarily associated with acquired myometrial weakness or whether it is an independent prerequisite for the development of adenomyosis remains to be determined.

The precise reason for myometrial hyperplasia/hyper trophy located around deep foci of endometrium is not known but may indicate either an attempt at controlling endometrial invagination of the myometrium or may simply represent smooth muscle bundles pushed aside by the ingrowing endometrium. By immunohistochemistry, the myometrium surrounding the ectopic endometrium, whether diffuse (adenomyosis) or focal (adenomyoma), contains no abnormalities. Indeed, smooth muscle cells in adenomyotic foci, normal myometrium and leiomyomata (coexistent or not with adenomyosis) are all rich in actin and desmin (Table I).

There are several animal models for the study of pathogenesis of adenomyosis. In one, intrauterine isografts of anterior pituitary mice lead to the development of adenomyosis (Jeffcoat and Potter, 1934). Prolactin may amplify this event, for the isograft-free horn contained comparatively less developed adenomyosis. Whereas ovariec tomy prevented, oestradiol benzoate stimulated, the development of adenomyosis in this animal model. In another model, mice treated prenatally with high doses of diethylstilboestrol (DES) developed adenomyosis. It appears that certain strains of mice are prone to develop adenomyosis in response to high concentrations of prolactin, oestrogens and progestogens. More recently, Ficicioglu et al. (1995) induced adenomyosis in non-castrated rats with hyperpro lactinaemia. The authors suggested that high prolactin concentrations cause myometrial degeneration in the presence of ovarian steroids which may result in myometrial weakness and subsequent myometrial invasion by the endometrial basalis. Of interest were the observations of Mori and Nagasawa (1983) in mice in which myometrial invasion by stromal fibroblasts along the branches of blood vessels preceded invagination of endometrial glands. In another study, Sakamoto et al. (1992) induced a high rate of uterine adenomyosis in mice by ectopic pituitary isografts. DNA-synthesizing activities and related enzymes, i.e. thymidylate synthetase and thymidine kinase, were markedly increased in adenomyosis compared to control uteri.
In the same experimental animal model, the finding of the small molecular weight matrix metalloproteinase was suggested to play a role in the development of adenomyosis at the level of gene transcription, activation and inhibition (Mori et al., 1996). Certain experimental observations suggested that some hereditary factors may be involved in the pathogenesis of adenomyosis. For example, the uteri of recombinant inbred SMXA mice develop spontaneously histological changes similar to adenomyosis and contain tenascin around adenomyotic glands (Kida, 1994). These observations together with the biological property of tenascin detailed earlier in this article are consistent with the endometrial origin of adenomyosis and the intramyometrial invagination concept of a genetically predisposed myometrium. Also, compared to SMXA mice, the uteri of F1 mice, a strain between SMXA and NJL strains, contain even more prominent spontaneous changes resembling human adenomyosis. Whether heredity is an important factor in adenomyosis in the human remains to be determined.

The de-novo origin of adenomyosis from Müllerian remains in extraterine sites seems to be supported by the observation of adenomyosis in the rectovaginal septum. Endometrial glands and stroma associated with smooth muscle cell hypertrophy may be found in this location forming adenomyotic nodules (Nisolle and Donnez, 1997). Although these nodules may develop as a result of invaginating peritoneal endometriosis, the Müllerian remains origin is favoured by some. According to Nisolle and Donnez (1997), in most cases adenomyotic nodules are located deep in the septum and occasionally in the muscularis propria of the rectum far from the pelvic peritoneum. Coexpression of vimentin and cytokeratin in endometrium whether lining the endometrial cavity or located within adenomyotic foci is typical of Müllerian-derived tissue. Morphologically and receptor content-wise, rectovaginal adenomyosis is identical to its intramyometrial counterpart, including poor or no response to postovulatory progestational stimuli. Despite large doses of exogenous progesterational agents given to women with rectovaginal adenomyosis to produce secretory transformation, hormonal therapy is poor. Obtaining definite cure of rectovaginal lesion by surgery is suggestive also of a metaplastic denovo process from Müllerian remains in that location rather than implantation/invagination of peritoneal endometriosis.

Admittedly, there are many more questions than answers with respect to the precise origin and pathogenic mechanism(s) of adenomyosis. Experimental and human studies are needed to shed light onto the pathophysiology of this challenging condition of the female genital tract.

**Incidence/predisposing factors**

The frequency of adenomyosis reported in the literature ranges from 5 to 70% (Azziz, 1989), and is largely dependent on how thoroughly the uterus is sampled, the histological criteria for making the diagnosis of adenomyosis and the selection of specimens to be evaluated. The more sections taken from a given specimen, the higher the frequency. For example, when three routine sections are taken, 31% of hysterectomy specimens contained adenomyosis and at six sections the rate increased to 61% (Bird et al., 1972). Using stringent diagnostic criteria, e.g. deeper than 25% of myometrial thickness, yields lower adenomyotic rates than if more superficially located glands are considered. Uteri removed because of symptoms contain higher rates of adenomyosis than those without symptoms. Even in the latter cases, the rates vary from 19% (Lee et al., 1984) in hysterectomy specimens to 57% in uteri examined at autopsy (Emge, 1962).

The vast majority of cases (80%) are reported in women aged 40 and 50 years old (Bird et al., 1972) and are associated with the most severe symptoms. The remainder of cases are observed in women younger than 39 years with relatively mild or no symptoms and in women older than 60 years of age (Benson and Sneeden, 1958).

Nearly all cases (90%) of adenomyotic uteri occur in multiparous women (Lee et al., 1984); it is not clear whether the condition is more prevalent in white than in black women (Israel and Woutersz, 1959; Mathur et al., 1962). Prior Caesarean section and obesity are not predisposing factors (Benson and Sneeden, 1958; Bird et al., 1972; Harris et al., 1985).

Tamoxifen in treated postmenopausal women seems to reactivate pre-existing adenomyosis, which leads to an increase in myometrial volume and uterine size (Ugwumadu et al., 1993; Cohen et al., 1995). Adenomyosis has been reported in 60% of 14 postmenopausal women on chronic tamoxifen therapy who eventually received hysterectomy for unrelated indications (Cohen et al., 1995).

**Clinical features**

About 35% of adenomyotic cases are asymptomatic (Benson and Sneeden, 1958); in the remaining cases, the most frequent symptoms are menorrhagia (50%), dysmenorrhoea (30%) and metrorrhagia (20%). Occasionally, dyspareunia may be an additional complaint. The frequency and severity of symptoms correlate with the extent (Benson and Sneeden, 1958) and depth (Nishida, 1991) of adenomyosis. The precise cause of menorrhagia in these patients is not known. It
may be due to poor contractibility of the adenomyotic uterus and compression of the endometrium by submucous adenomyomata or leiomyomata. Mefenamic acid administration can reduce blood loss suggesting that prostaglandins (F2α) may also play a role in the greater degree of bleeding loss in women with adenomyosis (Azziz, 1989). Other factors may be anovulation, hyperplasia and rarely adenocarcinoma. Dysmenorrhoea is due to uterine irritability which in turn is secondary to increased amounts of blood loss. Not all investigators have demonstrated adenomyosis-related symptoms. For example, in one study of 136 patients with histologically verified adenomyosis, symptoms were variable, non-specific and according to the investigators were related to the associated pathologies such as leiomyomata, endometriosis, polyps, etc. rather than adenomyosis (Nikkanen and Punnonen, 1980). In another study carried out prospectively, there were no differences in either the frequency or severity of dysmenorrhoea and pelvic pain between 28 women with adenomyosis and 157 ‘controls’ (Kilkku et al., 1984). A study of 23 women with uterine adenomyosis found no qualitative differences in the spontaneous mobility of isolated myometrial tissue throughout the menstrual cycle from normal regenerative and leiomyomatous uteri (Martinez-Mir et al., 1990). The mobility pattern was of low amplitude and high frequency of spontaneous contractions during the proliferative phase; both changes were amplified in the secretory phase. Histamine-produced myometrial contractions were similar in all myometrial tissues investigated (Martinez-Mir et al., 1990).

### Associated pathology

Up to 80% of adenomyotic uteri contain associated pathology. The most frequent one is leiomyomata (Azziz, 1989). Endometrial polyps (2.3%), hyperplasia without and with atypia as well as adenocarcinoma appear more frequent in patients with adenomyosis than in the general population (Table II). In one study, 60% of uteri with endometrial carcinoma contained coexistent adenomyosis compared to 39% in control uteri (Marcus, 1961). However, the presence of adenomyosis has no adverse (negative) influence on the prognosis of endometrial carcinoma (Marcus, 1961; Hall et al., 1984). Pelvic endometriosis is observed only in 6–20% of women with adenomyosis and in all likelihood the former is unrelated to the latter.

### Adenomyosis and pregnancy

Although adenomyosis occurs relatively frequently in pregnancy [27 of 151 (17%) of Caesarean hysterectomy specimens] it is not a major cause of obstetric or surgical complications. A review of 80 years of literature yielded only 29 reports of complications, mainly uterine rupture and perforation associated with adenomyosis (Azziz, 1986).

### Table II. Associated pathology and adenomyosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyoma</td>
<td>35–55</td>
</tr>
<tr>
<td>Pelvic endometriosis</td>
<td>6–20</td>
</tr>
<tr>
<td>Salpingitis isthmica nodosa</td>
<td>1.4–19.8</td>
</tr>
<tr>
<td>Endometrial polyps</td>
<td>2.3</td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>7.0</td>
</tr>
<tr>
<td>(types not specified)</td>
<td></td>
</tr>
<tr>
<td>Endometrial hyperplasia with atypia</td>
<td>3.5</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1.4</td>
</tr>
</tbody>
</table>

### Diagnosis

The clinical diagnosis of adenomyosis is only suggestive at best (50%) (Hayata and Kawashima, 1987) and most often is either not made (75%) (Owalabi and Strickler, 1977; Azziz, 1989) or overdiagnosed (35%) (Lee et al., 1984). Menorrhagia and dysmenorrhoea in a multiparous woman in her late 40s/early 50s are suggestive but not diagnostic of adenomyosis. The uterus may be diffusely enlarged (12 weeks of gestational size), soft and tender on palpation.

Hysterosalpingography for diagnosing adenomyosis is not recommended because it misses 75% of the cases (Marshak and Eliasoph, 1955) and is expensive. Similarly, ultrasonography is of questionable diagnostic value. Experience with endovaginal ultrasonography seems to indicate a better diagnostic accuracy than grey-scale ultrasound with a sensitivity of 87%, a specificity of 98%, a positive predictive value of 74% and a negative predictive value of 99% (Fedele et al., 1992). Adenomyosis in tamoxifen-treated women appears as irregularly distributed microcysts beneath the endometrium and in the myometrium masquerading as increased endometrial thickness on transvaginal ultrasonography (Goldstein, 1994; Perrot et al., 1994) and leads to undue anxiety and unnecessary endometrial biopsies. The best radiological means so far is magnetic resonance imaging (MRI) although experience is limited. Low signal intensity myometrium surrounds normal, high-signal intensity endometrium. In other cases, irregular cystic spaces in the myometrium give a honeycomb-type appearance of adenomyosis. Blood CA125 determinations have provided inconsistent results so far (Takahashi et al., 1985; Halila et al., 1987) have little, if
Figure 3. Diffuse adenomyosis of anterior wall of uterus. Note coarsely trabeculated, diffusely hypertrophied myometrium stippled with foci of ectopic endometrium. Original magnification ×4.

Figure 4. Adenomyoma (focal adenomyosis) made of cystically dilated endometrial glands and hypertrophied smooth muscle. Typical of adenomyoma, its margin is indistinct from the surrounding normal myometrium. Original magnification ×40.

any, diagnostic value. More recently, myometrial biopsies of the posterior uterine wall were performed using biopsy needle (Bohlman et al., 1987) or resectoscope (McCausland, 1992). The upper third posterior myometrial wall biopsy without important bleeding revealed adenomyosis in five of 45 women (11%) aged 40 years or younger who were undergoing laparoscopy or laparotomy for miscellaneous reasons (Pasquinucci et al., 1991). Alternatively, hysteroscopy-aided biopsy of the posterior uterine wall with a 5 mm loop electrode in 50 women with normal uterine cavity demonstrated adenomyosis in 66% of the cases (McCausland, 1992). Others found very low sensitivity of myometrial needle biopsy performed in 68 surgically removed uteri. The rates ranged between 8 and 18.7%; however, specificity was 100% (Popp et al., 1993). In two studies, MRI predicted adenomyosis in eight of eight patients (Mark et al., 1987) and in eight of 16 patients (Marshak and Eliasoph, 1955) whose disease was confirmed by histology. The principal diagnostic means for adenomyosis is histology of hysterectomy specimens.

Pathology

The characteristic gross appearance of adenomyosis is due to myometrial hypertrophy surrounding endometrial mucosa. When the whole myometrium or one of the myometrial walls is diffusely involved, the uterus is enlarged and globular. On cross-section, the haphazardly distributed hypertrophied muscular trabeculae surrounding foci of adenomyosis are apparent (Figure 3). The latter may on occasion contain brown-staining ‘old blood’ corresponding to hemolysed blood and haemosiderin pigment deposits (Azziz, 1989). The focally involved uterus with adenomyosis resembles a leiomyoma; the term adenomyoma is applied to this rather frequent presentation of adenomyosis (Figure 4). Since the process is not neoplastic, the term focal adenomyosis is preferred by Hendrickson and Kempson (1980). Since adenomyoma is often confused clinically with leiomyoma, a benign but neoplastic condition, we believe that the use of the term adenomyoma is acceptable. Typically, adenomyoma has poorly defined margins because they merge with the surrounding normal myometrium (Figure 5). In contrast, leiomyomata compress the surrounding myometrium and have clear-cut, well-circumscribed margins (Figures 6 and 7). The latter can be enucleated, whereas the former cannot.

Over the years, the author accumulated experience with a relatively large number of cases of adenomyosis (n = 50), endometriosis (n = 50) (unpublished data) and normal endometrium (n = 200) (Bergeron et al., 1988a,b; Ferenczy
Figure 5. Detail of poorly defined margin of adenomyoma. Unlike ordinary leiomyomata, such a lesion cannot be enucleated. Magnification: ×400.

Figure 6. Leiomyomata uteri with well-circumscribed margins contrast with adenomyoma shown in Figure 5. Original magnification ×4.

Figure 7. Histology of sharply defined margin of ordinary leiomyoma. Original magnification ×100.

and Bergeron, 1991; Ferenczy, 1994) in both ovulating and postmenopausal women.

Histologically and by immunohistochemistry, both the endometrial glands and stroma in foci of adenomyosis resemble the basalis endometrium (Figures 8 and 9 and Table I). It seldom responds to hormonal stimuli, a phenomenon which explains at least partly why one sees only occasionally haemorrhagic or reparative morphological events in foci of adenomyosis. The reason for an increased tendency for focal haemorrhage in deeply located adenomyotic foci is not understood (Sandberg and Cohn, 1962). In contrast, ectopic endometrium in foci of endometriosis often undergo cyclic changes including degeneration, bleeding and regeneration in all respects similar to the functionalis layer of the endometrium. The different frequency in menstrual-type changes between the two endometria are likely due to the relatively poor vascularization of the basalis-type adenomyotic endometrium compared to the richly vascularized functionalis-type endometrium in endometriosis. However, adenomyotic endometrium seems to retain its proliferative potential, to be the seat of endometrial growth and to be responsible for failure of providing amenorrhea or hypomenorrhoea following endometrial ablation (Haber and Ferenczy, 1993). Secretory transformation including stromal decidualization in foci of adenomyosis is seen mainly...
during gestation and exogenous progestational therapy, the changes being mediated by oestrogen and progesterone receptors (Table I). Progestational effect in non-gravid uterus occurs between 30 and 50% of adenomyotic foci (Mathur et al., 1962; Molitor, 1971). During intrauterine pregnancy, 57% of the articles reviewed by Azziz (1986) described decidualization. Others observed decidualization during pregnancy only in deeply located foci (at depth of two low power fields), whereas decidualization was absent or inconspicuous in foci located less than two low power fields from the basalis–myometrium junction (Sandberg and Cohn, 1962). Also, it is not unusual to find hyperplastic changes with or without atypia in adenomyosis associated with similar conditions in the overlying endometrium. Hyperplasia in adenomyotic foci may contain metaplastic changes of the glandular epithelium such as tubal metaplasia, squamous metaplasia (squamous mo- rules) and mucinous metaplasia. Adenocarcinoma may also involve foci of adenomyosis. When carcinoma is limited to adenomyotic foci, it should be considered intramucosal since it does not make the prognosis worse than the carcinoma for which the patient has had surgery. Whether adenocarcinomas located in both the overlying endometrium and foci of adenomyosis represent simultaneous primaries or extension of the former in adenomyotic foci is not possible to determine by histology. The latter hypothesis is preferable because adenocarcinoma in foci of adenomyosis without surface component is an extremely rare event (Colman and Rosenthal, 1959; Winkelman and Robinson, 1966).

**Treatment**

Suppressive hormonal therapies using oral contraceptives and progestational agents are of no value. GnRH agonist is given for 6 months to relieve symptoms (dysmenorrhea and menorrhagia) and decreases uterine volume; however, the symptoms reappear after discontinuation of leuprolide acetate therapy (Grow and Filer, 1991). Some women with superficial adenomyosis (<1 mm myometrial involvement) may theoretically benefit from hysteroscopic resection (McCausland, 1992). It remains to be seen whether all adenomyotic foci can be removed from these patients using this technique; if not, residual adenomyosis-related symptoms and signs will remain. Admittedly, the definitive therapeutic technique is hysterectomy.
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