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Case Report

Myometrial Hyperplasia Mimics the Clinical Presentation of Uterine Fibroids: A Report of 3 Cases

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Summary: The clinical diagnosis of fibroid uterus is based on physical examination findings and/or ultrasound. However, it is not uncommon for routine pathology examination to report no significant fibroids in such cases. Myometrial hyperplasia (MMH) is a structural variation with irregular zones of hypercellularity and increased nucleus/cell ratio that appears in adolescence, can progress during the childbearing years, and can sometimes cause grossly detectable bulges on pathologic examination. MMH can be inframucosal, intramural (microscopic), or subserosal. Three premenopausal women with a preoperative diagnosis of fibroids on pelvic examination, and/or sonograms, underwent hysterectomies. In all the 3 cases, the Myoma Index (number of fibroids × size of largest fibroid) indicated insignificant fibroids. The pathology simulating fibroids was firm, bulging inframucosal MMH. Firm, bulging MMH can mimic uterine fibroids on ultrasound and physical examination. In hysterectomies for fibroid uterus with a Myoma Index < 3.7, it is recommended that pathologists evaluate for MMH as the possible explanation for the findings on physical examination and/or ultrasound. **Key Words:** Fibroids—Leiomyoma—Myometrial hyperplasia—Benign uterine disease.

It is increasingly clear that myometrial morphology is heterogeneous and complex. The proportion of fibrous tissue varies regionally (1); and the stereotypical image of parallel muscle bundles has been augmented by an appreciation of the basketweave pattern (2,3). In 1985, an attempt was made to explain why magnetic resonance imaging shows a junctional low-intensity zone, but no distinctive histology was reported (4). In 1991, a similar effort restricted its focus to hysterectomies for benign disease, and morphometry showed a 3-fold increase in relative nuclear area in the junctional zone, interpreted as myometrial zonal differentiation (5). Subsequent radiologic studies demonstrated a deviation termed junctional zone hyperplasia (6). An independent line of inquiry focused on "relatively blue" areas seen in routine sections of hysterectomies for benign disease (7). Morphometry showed irregular zones with increased cellularity and nucleus/cell ratio, compared to normal outer myometrium in the same uterus; which was named myometrial hyperplasia (MMH) in that article. In retrospect, inframucosal MMH (7) corresponds to the junctional zone (5) seen on magnetic resonance imaging. Striking inframucosal MMH may correspond to

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junctional zone hyperplasia (5–7). However, MMH is not restricted to the junctional zone. MMH can also be intramural (microscopic), or subserosal. Our observations on MMH since 1995 are summarized in the diagram in Figure 1.

Inframucosal MMH, like osteoporosis, is a hormonally sensitive structural variation with onset in adolescence and slow progression over decades in some women, eventually producing symptoms in those who are most affected (7–11). In these cases, we postulate pressure effects caused by firm, bulging inframucosal MMH, explain outward bulges, inward bulges, and vascular ectasia similar to the pressure effects caused by fibroids (11–13).

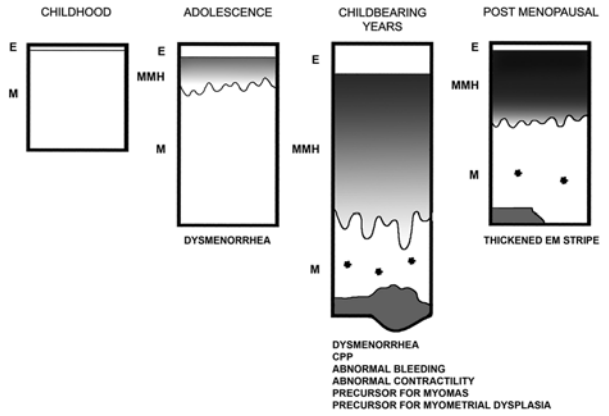

FIG. 1. Diagram depicting the natural history of inframucosal, intramural, and subserosal MMH, based on observations since 1995 (7). MMH is not a congenital anatomic variation, and is not observed prior to puberty (childhood). Inframucosal MMH is first seen after onset of menses just beneath the endomyometrial junction, and can be seen 5 mm deep in the junction by age 18 (8). Intramural and subserosal MMH have not been reported in adolescence (adolescence). In adulthood, inframucosal MMH goes deeper in the wall, and tends to be more hypercellular. The growth zone appears to be at the endomyometrial junction (8,9). Deeper inframucosal MMH tends to be less cellular, and tends to fade away gradually and irregularly, interpreted as senescence (3,7,9). Inframucosal MMH can be bulky, firm, and bulging; causing pressure effects similar to those seen in fibroid uteri (11–13); possibly explaining abnormal bleeding in some cases. Deep inframucosal MMH can be seen on magnetic resonance imaging and interpreted as junctional zone hyperplasia (5–7) (childbearing years). Microscopic foci of intramural MMH (*) appear in adulthood (7,9,11); and their only significance may be as precursors for leiomyomas (9). Inframucosal and subserosal MMH can also be precursors for myomas (9,10). MMH may also rarely progress to myometrial dysplasia (10). Subserosal MMH also appears in adulthood. It can be focal or diffuse (7,11). Florid examples may be palpable on physical examination as serosal bulges, simulating fibroids. Subserosal ridges may sometimes resist outward bulging caused by inframucosal MMH, and contribute to the pathogenesis of dysmenorrhea and chronic pelvic pain (11). After the menopause, shrinkage of myometrial cells occurs resulting in a higher nucleus/cell ratio, so inframucosal MMH appears darker on scanning magnification). It may contribute to thickened endometrial stripes. Inframucosal MMH shrinks more than normal myometrium, so it usually appears to go less deep in the wall after menopause (postmenopausal). *indicates intramural (microscopic) MMH; CPP, chronic pelvic pain; E, endometrium; M, myometrium; MMH, myometrial hyperplasia.

We now report the intriguing finding of MMH mimicry of uterine fibroids diagnosed clinically. Three individuals had pelvic examinations and prepreoperative sonograms indicative of fibroids. Thorough pathologic examination, however, demonstrated that the irregular zones of firm, bulging, and microscopically hypercellular myometrial tissue responsible for the clinical and sonographic findings was actually inframucosal MMH.

CASE REPORTS

The individual subjects presented here, and the 3 treating gynecologists, have given written consent to be included in this report. No case had a history of cesarean section or other uterine surgical procedure.

A 51-yr-old, white G1P1 woman underwent robotic-assisted laparoscopic hysterectomy for "symptomatic uterine fibroids causing intractable menorrhagia." The endometrial stripe was noted by the sonographer to be 20 mm thick (Fig. 2A). A $4 \times 4 \times 0.7$ cm lesion was noted in the myometrium, just under the endometrium. On pelvic examination, the uterus was bulky, 8 wk in size. Despite preoperative leuprolide, the uterus was still bulky and 8 wk in size at surgery. It weighed 162 g. A posterior inward bulge was identified on gross examination (Fig. 2B). The disordered proliferative endometrium was only 10 mm thick (Fig. 2C). On microscopic examination, MMH was seen 17 mm deep in the wall, causing the inward bulge. Innermost, inward bulging inframucosal MMH was hypercellular with increased nucleus/cell ratio (Fig. 2D) as compared to normal outer myometrium (Fig. 2E); accounting for the other 10 mm of the thickened stripe. Deeper, less cellular inframucosal MMH, which we interpret as senescent, was not detected by ultrasound. A 4-mm fibroid was present.

A 49-yr-old premenopausal white G1P0 underwent a supracervical hysterectomy for fibroids. She had complained of constant pain for 2 yr. Ultrasound demonstrated a bulky uterus, with a 1.6×1.4 cm fibroid protruding through the posterior endometrium. The resected uterus weighed 84 g. Inframucosal MMH was noted on pathology examination, accounting for the "fibroid" seen by ultrasound (Fig. 2F). Inframucosal MMH was hypercellular with increased nucleus/cell ratio (Fig. 2G) as compared to the normal outer myometrium (Fig. 2H). There was vascular ectasia and edema of the outer

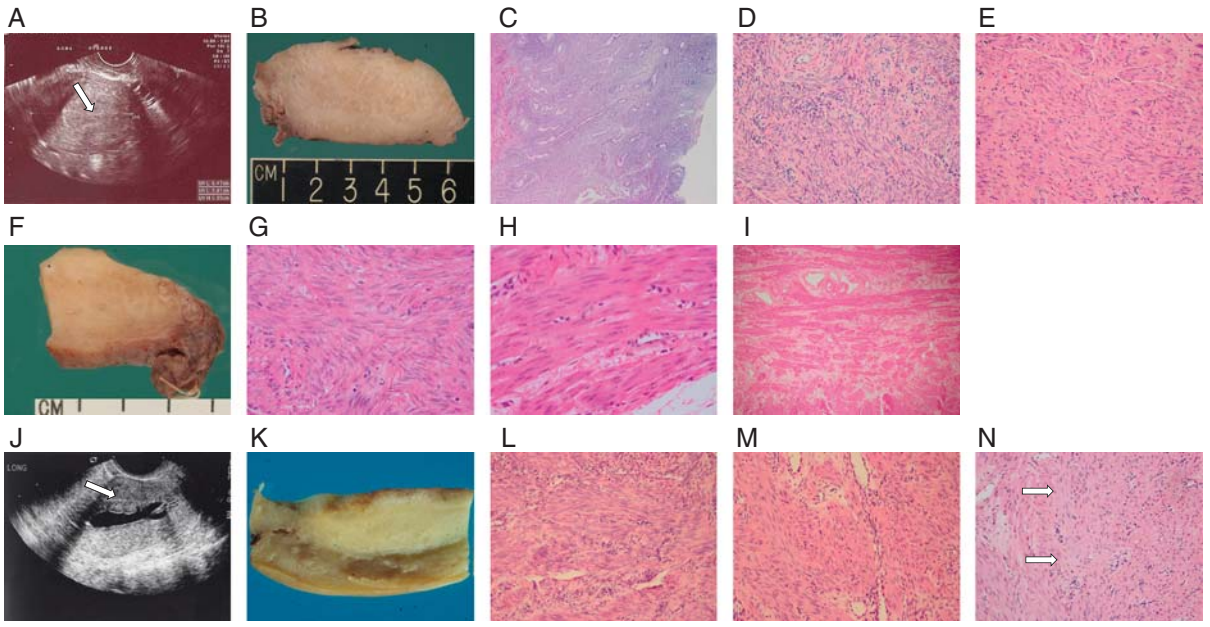

FIG. 2. (A) Sonogram in Case 1 suggested inframucosal fibroid, (arrow) and 20 mm thick endometrial stripe to the sonographers (observed as a white line); (B) gross photo of area with sonographic abnormality—inward bulge was firm myometrial hyperplasia (MMH), with no fibroid; (C) endometrium is 5 mm thick, both anteriorly and posteriorly, accounting for only 10 mm of thickened stripe; (D) inner myometrium is hypercellular with increased nucleus/cell ratio, accounting for deep half of the thick stripe; (E) normal myometrium. (F) Sonogram in Case 2 suggested fibroid protruding into the lumen in posterior wall, and gross photo shows bulge of pale firm inner MMH corresponding to sonogram; (G) inner MMH is hypercellular, with increased nucleus/cell ratio, compared to (H) normal myometrium, with (I) vascular ectasia and edema, due to increased intramural pressure caused by MMH. (J) Sonohysterogram in Case 3 was interpreted as showing a fibroid on anterior uterus (arrow); (K) pale firm inner MMH accounts for sonographic finding; (L) inframucosal MMH has increased cellularity and nucleus/cell ratio compared to (M) normal myometrium. (N) Deeper, "older" inframucosal MMH "fades away" irregularly at its interface with normal outer myometrium (arrows). When there is persistent gestational myometrial hyperplasia (chronic subinvolution) of the outer myometrium in abnormally enlarged uteri (myometrial hypertrophy), this interface is even more indistinct.

myometrium, consistent with increased intramural pressure caused by the inframucosal MMH (Fig. 2I) (10). Four fibroids, measuring 2 to 6 mm, were found.

A 31-yr-old white premenopausal G3P2 underwent a supracervical hysterectomy, Halban culdoplasty, abdominal-sacral colpopexy, and a Burch procedure for cystocele, rectocele, and stress urinary incontinence. Sonohysterogram had noted an irregular contour of the anterior endometrium, bulging into the uterine cavity. This 1×1.5 cm mass was interpreted as a fibroid (Fig. 2J). The resected uterus weighed 64 g. Pathology examination revealed no fibroids. However, firm pale inframucosal MMH was noted, best seen after thorough formalin fixation, in the area seen on the sonohysterogram (Fig. 2K). Microscopically, it was hypercellular with increased nucleus/cell ratio (Fig. 2L) as compared to the normal outer myometrium (Fig. 2M). The deepest, "oldest" inframucosal MMH, not visible on the sonohysterogram, had a subtle irregular interface with outer normal myometrium (Fig. 2N).

DISCUSSION

The ability of MMH to produce bulges on gross pathology examination was noted in the original report of its histologic and morphometric features (7). These 3 cases now demonstrate that firm, bulging irregular inframucosal zones of myometrial hypercellularity with an increased nucleus/cell ratio (inframucosal MMH), can masquerade as fibroids on ultrasound imaging; and can also be responsible for sonographic impressions of a bulky uterus. Inframucosal MMH can also contribute to "thickened endometrial stripes." We reviewed all the imaging reports. Two of the images were independently reviewed and interpretations were confirmed by experts. The third was not available for review. The impression of a bulky uterus on palpation in these cases was made by very experienced gynecologists.

A study published in 1990 noted no mention of fibroids in routine pathology reports in 33% of hysterectomies for fibroid uterus (14). Furthermore, incidental fibroids were noted in benign hysterectomies carried out for other diagnostic indications. The

average number of incidental fibroids in these other uteri, after slicing uteri at 2-mm intervals, was 4; and the average size of the largest fibroid was 0.9 cm. On the basis of these findings and our subsequent experience, we propose that the product of size and number be used to calculate a Myoma Index, and that benign hysterectomies with Myoma Index <3.7 be evaluated for MMH as the possible etiology for signs and symptoms simulating fibroids. All 3 of the current cases have Myoma Index of <3.7, and in 1 case it was 0. If a uterus has less fibroid tissue than the average case of "incidental fibroids," we think this is a good first step towards trying to provide an objective measure of the significance of a few small myomas in a clinically fibroid uterus. Although the Myoma Index is a crude tool, at least it is objective; and this published data qualifies as an evidence-based criterion. A recent prospective study found Myoma Index of <3.7 in 20% of hysterectomies for fibroids (11).

Clinical, gross, and microscopic criteria for identifying firm bulging inframucosal MMH are summarized in Table 1. These criteria permit diagnosis of firm bulging inframucosal MMH in: (A) cases without any myomas or adenomyosis; (B) cases with a few small myomas (low Myoma Index); (C) cases with focal microscopic superficial adenomyosis, insufficient to account for a bulky uterus with pressure effects.

Despite the popularity of the term "submucous myoma," the term inframucosal MMH is preferable to "submucosal MMH." Although both the terms mean "underneath" the mucosa; submucosa has its own anatomic meaning as referring to a layer of the wall between the mucosa and the muscular wall. Unlike the gastrointestinal tract, there is no such layer in the uterus, and the absence of a true submucosa in the uterus is the major factor in the pathogenesis of inframucosal MMH (7). The observation of smooth muscle accretion at the endomyometrial junction dates back to Bird and Willis (15), which antedated our observation that the growth zone of inframucosal MMH in adolescent and young adult uteri appears to be at the endomyometrial junction (8).

A diagnosis of clinically significant inframucosal MMH can be made by first noting the appearance of the slides, where MMH may appear relatively blue. This is then confirmed on scanning magnification, and high-power examination at $400\times$ can then document increased cellularity and nucleus/cell ratio. "Obvious" microscopic differences correlate with statistically significant morphometric differences (7). Although cellular leiomyomas have similar hypercellularity with increased nucleus/cell ratio, they are identified on gross examination as tumor nodules.

TABLE 1. *Criteria: clinically significant inframucosal myometrial hyperplasia*

Microscopic
Relatively blue inner myometrium beneath endomyometrial junction on scanning magnification
Irregular zone of myometrial hypercellularity and increased nucleus cell ratio compared to outer normal myometrium—in the same uterus. May be ≥ 15 mm deep into the wall. Subtle fading appearance of lower border
The following pressure effects may be seen
Vascular ectasia and edema of outer myometrium (may cause outward bulge)
Vascular ectasia within a zone of inner MMH (might extend into endometrium)*
Inward bulges of inframucosal MMH (can be micronodular projections into overlying endometrium)
Macroscopic
Pale, firm inner myometrium compared to brown or brown-red (congested) outer myometrium† (11)
Inward bulges of inframucosal MMH
Outward bulges of normal myometrium due to pressure effects by inner wall MMH*
Occasional cases may exhibit vascular ectasia of outer myometrium
Clinical/radiologic
Bulky uterus on ultrasound and/or physical exam
Circumscribed zone just beneath the endometrium visualized by ultrasound
Inward bulge visualized by ultrasound
Unexplained thickened endometrial stripe
Junctional zone hyperplasia visualized by magnetic resonance imaging (no evidence of deep adenomyosis on microscopic exam)

*Subserosal ridges, gross or even microscopic sometimes resist outward bulging, redirecting pressure inwards (11).

†In poorly involuted uterus, persistent gestational myometrial hyperplasia may attenuate relative paleness of firm bulging inframucosal MMH.

MMH indicates myometrial hyperplasia.

The pathologist may also observe that inframucosal MMH may cause pressure effects on gross and microscopic examination, such as inward and outward bulges, and vascular ectasia and edema of outer myometrium, resembling those seen in fibroid uteri (11–13). Postmenopausal MMH appears "bluer" because of a higher nucleus/cell ratio (Fig. 1) caused by myometrial cell shrinkage, but this shrinkage tends to reduce pressure effects.

Inframucosal MMH may be firm to palpation, and may also be pale yellow-white in color; but these findings can be easily missed on initial gross examination. Microscopic review and calculation of Myoma Index should lead to reexamination of the gross specimen after thorough formalin fixation, because paleness may not have been conspicuous in fresh or partly fixed specimens; and palpation for firm areas is not part of routine practice in all laboratories.

Relative paleness may also be inconspicuous in abnormally large uteri (16–20), even when there is firmness to palpation and sonographic detection of MMH (Fig. 2B). This reduced contrast may reflect persistent gestational MMH, which we regard as the proper definition of chronic subinvolution (17).

Part of the challenge in recognizing inframucosal MMH, even in the well-fixed specimen, is that the typical case of inframucosal MMH is not well demarcated (7). Deeper MMH has lower cellularity, and tends to have increased collagen; consistent with a senescent phase of MMH (3,7,9). Thus, inframucosal MMH usually fades away gradually and irregularly as it interfaces with underlying normal myometrium (Fig. 2N).

This "fading away" of old MMH fits well with the morphometric finding that some examples of MMH have relatively high nuclear size, as compared to normal myometrium in the same uterus; whereas other examples have significantly lower nuclear size (7). Larger nuclear size is consistent with an actively growing phase of MMH, whereas lower nuclear size is consistent with a senescent phase. These nuclear differences can be more obvious with immunostains for estrogen receptors (unpublished data).

Morphometry is not necessary in routine practice. "Obvious" differences between MMH and normal myometrium have been shown to have statistically significant differences on morphometry (7); and subtle differences (Fig. 2N) are usually not detectable on sonograms. Nevertheless, consideration of the morphometric data may help to explain clinicopathologic and sonographic-pathologic correlations.

Although cellularity varied 4-fold in normal myometrium (7), nucleus/cell ratio in normal myometrium was always <0.4, whereas nucleus/cell ratio of MMH was always >0.4. Subsequent experience suggests that the nucleus/cell ratio of inframucosal MMH after long-term Depo-Provera associated with full-blown myometrial hypertrophy of >300 g may be lower than usually observed (7), even though it is still obviously higher than nucleus/cell ratio of normal myometrium in the same uterus. Similarly, leuprolide treatment to shrink the uterus so as to facilitate surgical removal may be associated with a higher nucleus/cell ratio in normal myometrium than previously observed; but is still obviously lower than nucleus/cell ratio of MMH in the same uterus (7).

Although one can generally detect obvious differences in nucleus/cell ratio on routine hematoxylin and eosin stains, by noting "relative blueness," (7) increased collagen can lead to more widely spaced nuclei, interfering with routine assessment of nucleus/cell ratio. The point counting morphometric method (7) corrects for points that fall on interstitial collagen and vessels. In the absence of morphometry, a trichrome stain can be helpful in routine practice to confirm the impression of increased nucleus/cell ratio, when indicated (3). The trichrome stain can also distinguish whether microscopic "pink" foci represent focal hypertrophy of smooth muscle cells or microscopic foci of fibrous degeneration in MMH (3,10).

"Older," deeper, less cellular MMH at some point becomes undetectable on the sonogram, so that part of a "thickened endometrial stripe" can be the most hypercellular portion of inframucosal MMH closest to the endomyometrial junction, whereas deeper senescent inframucosal MMH can be sonographically undetectable (Case 1).

This also explains how firm bulging inframucosal MMH can simulate a fibroid on sonograms (Cases 1–3). The point at which "older," deeper, less cellular MMH becomes sonographically undetectable can be interpreted by the sonographer as the interface between a fibroid and adjacent myometrium. Even in Case 3, with better demarcated inframucosal MMH in the well-fixed gross specimen, MMH went deeper microscopically than was apparent on both the sonohysterogram and gross examination.

It is pertinent to the present cases that normal outer myometrium varies 4-fold in cellularity (7). This appears to be related in part to age and hormonal status (7). However, some of this variation may be related to uterine weight, which varies in relation to age and parity (16). It is universally acknowledged that during pregnancy there is both gestational hypertrophy of myometrial cells, and gestational hyperplasia of myometrial cells. Postpartum, gestational hypertrophy of smooth muscle cells gradually regresses; but regression of gestational hyperplasia of myometrial cells seems to be highly variable. Thus, some uteri shrink back to normal size, but others remain quite enlarged, possibly because of deficient postpartum apoptosis, qualifying for a designation of "myometrial hypertrophy," based on the criterion of excess weight (16–20). Regardless of whether excess weight meets modern criteria for myometrial hypertrophy (20), failure to shrink back to normal may qualify as the true definition of chronic subinvolution (17). This report demonstrates that enlarged uterine weight can hinder detection of clinically significant MMH.

MMH is defined differently than myometrial hypertrophy. The modern definition of nongestational myometrial hypertrophy is based on uterine weight, taking age and parity into account; regardless of microscopic findings (20). Our 3 uteri weighed 162 g (51 yr old P1), 84 g (49 yr old P0), and 64 g (31 yr old P3); none of which qualifies as myometrial hypertrophy by modern criteria, which requires a weight of 201 g for P1-3 uteri or 130 g for P0 uteri (20). Thus, firm bulging inframucosal MMH with associated pressure effects may be present in uteri that do not qualify as myometrial hypertrophy.

Current pathology textbooks do not suggest that myometrial hypertrophy is a legitimate explanation for symptoms leading to hysterectomy (2,20); although this was a view in the past. Lewis et al. (18) used the threshold of 120 g to debunk myometrial hypertrophy as a legitimate explanation for the syndrome of abnormal bleeding in perimenopausal women with an enlarged uterus on physical examination. Honore (19) used 125 g as the definition for myometrial hypertrophy, noting that most cases of myometrial hypertrophy were <150 g. Larger uterine weights were usually due to adenomyosis and/or fibroids.

We do not suggest in this paper that myometrial hypertrophy causes signs and symptoms that lead to hysterectomy. On the contrary, we suggest that myometrial hypertrophy may tend to interfere with detection of irregular zones of MMH with increased celluarity and nucleus/cell ratio, which can cause signs and symptoms that simulate fibroid uteri, leading to hysterectomy.

From our perspective, lower thresholds used in the past to define myometrial hypertrophy may be more appropriate in judging when uterine enlargement may interfere with gross detection of firm bulging inframucosal MMH. Our Case 1—with a uterine weight of 162 g and P1 status at age 51—would have been regarded as larger than expected according to the data of Langlois (16)—who noted that average uterine weight for P1 women was 80 to 100 g, and average uterine weight for women aged 50-60 was 84 g. This amount of enlargement was enough to make it more difficult to detect inframucosal MMH on gross examination (compare Figs. 2B to 2F and to 2K), even after thorough formalin fixation. We believe that residual gestational hyperplasia of myometrial cells led to decreased color contrast between inframucosal MMH and outer myometrium; although firm bulging inframucosal MMH was still detectable on the sonogram, palpable in the gross specimen, and visible on microscopic examination.

Also in the differential with myometrial hypertrophy and MMH is diffuse uterine leiomyomatosis (21). As with the distinction of seedling myomas from intramural microscopic MMH, and the distinction of cellular leiomyoma from inframucosal MMH (7,9,14); the objective criteria used to distinguish diffuse uterine leiomyomatosis from MMH are nodularity, circumscription, and compression of adjacent myometrium.

Deep extensive adenomyosis can cause firm bulges and pressure effects, but was excluded in these 3 cases by extensive sampling—4 sections of full-thickness endomyometrium, 2 anterior and 2 posterior. In our experience of identifying MMH in routine hysterectomies since 1995 (7), focal superficial microscopic adenomyosis is often a marker for associated bulky inframucosal MMH that is more likely to be responsible for the patient's signs and symptoms, leading to hysterectomy. No adenomyosis was present in the cases being reported here.

Striking disturbances in myometrial morphology can be iatrogenic, due to caesarian section, ablation, or endomyometrial resection (3). None of these factors led to the inframucosal MMH simulating fibroids in these 3 cases.

Diffusely hypercellular myometrium with increased nucleus/cell ratio can be seen as a result of myometrial cell shrinkage in postmenopausal atrophy (7); but distinction from MMH is still straightforward. MMH is an irregular zone of hypercellularity that differs from myometrium elsewhere in the same uterus, even after menopause (Fig. 1).

Although the clinical significance of MMH is poorly understood, this report bolsters the light microscopic, macroscopic, and morphometric evidence that MMH differs from normal myometrium elsewhere in the same uterus. Recent work has suggested a possible role for MMH in the pathogenesis of altered wound healing leading to hysterectomy for abnormal bleeding (3) and as a precursor for fibroids (9). The origin of MMH, its clinical significance, and its basic biology all merit considerable further scrutiny.

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