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POSTABLATION NEUROMA OF THE MYOMETRIUM – A REPORT OF 5 CASES

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Abstract

When hysterectomy is performed for chronic pelvic pain, routine pathology examination often provides no explanation. However, analysis of small uterine nerves using immunostains may help to address this deficiency. Small uterine nerves tend to be sparse or absent in wide areas of normal myometrium. Some studies of uterine nerves have suggested that endometriosis, adenomyosis, and fibroids are not inherently painful, with increased small nerves in the inner uterine wall associated with the history of pelvic pain. Although such areas may appear normal on Hematoxylin and Eosin (H&E), we have found a subtle inner wall lesion termed inner myometrial elastosis, best detected with trichrome or elastic stains, which may be a reaction to microscopic tears of inner myometrium. Such tears may induce increased inner wall innervation via the generation of Nerve Growth Factor in granulation tissue. In the course of studying uterine nerves with immunostains, we found 5 cases with florid nerve proliferation, after deep endometrial ablation for abnormal uterine bleeding led to increased pelvic pain. We suggest that immunostains for postablation neuromas should be done in hysterectomies when pelvic pain increases after endometrial ablation. This may offer gynecologists and their patients an objective finding with a rational, scientific explanation for the pelvic pain.

Key words: chronic pelvic pain, neuroma, endometrial ablation

1.1 INTRODUCTION

Chronic pelvic pain is common, and may lead to hysterectomy. Reasons for chronic pelvic pain include endometriosis, adenomyosis, fibroids, pelvic adhesions, pelvic inflammatory disease, ovarian cysts, and polycystic ovaries, but oftentimes an explanation is lacking (1-4). Recent studies have suggested that an increase in innervation of the inner myometrium and endometrium may play a role in the pathogenesis of chronic pelvic pain (2,3,5). This led us to evaluate our own experience, and to consider whether pathologists should routinely evaluate for uterine nerves in hysterectomies for pelvic pain.

In 2005, Atwal et al demonstrated an increased number of nerve fibers in the inner wall in women with advanced endometriosis (2). They also found increased nerve fibers in women with chronic pelvic pain but without endometriosis. Since their control group was uteri removed for painless conditions, this suggested that the endometriosis itself was not the cause of pain. In 2010 Zhang et al found increased nerves in the endometrium and inner myometrium in women with painful adenomyosis and painful fibroids (3). Again, the increased nerves were not in the lesions themselves, but in adjacent tissues.

Large areas of normal myometrium can lack demonstrable nerve fibers (5). Normal uterine nerves in nulliparous women are mainly in three distributions: the subserosa, in sparse neurovascular bundles coursing through the myometrium, and at the endomyometrial junction (5). Based on prior literature (2,3,5) and our personal experience, we classify 5 or more nerve fibers/field at 200x magnification as abnormally increased (Figure 1a).

It has been reported that 30% of multiparous uteri had foci of abnormal clusters of small nerves, called microneuromas, whose clinical significance is not established (5). Microneuromatous clusters may have 10 or more nerve fibers. In our experience (unpublished), microneuromas are associated with naturally occurring outer wall scars (fibrosis uteri) (Figures 1b,c). Fibrosis uteri generally has a component of elastosis, and it was a matter of common knowledge 40 years ago that this was a marker for parity; but many recent texts have failed to cite the references to naturally occurring myometrial scars that date back more than a century (6,7).

Since starting to evaluate hysterectomies for pain with immunostains for nerves, we encountered 5 cases in a single year with a striking pattern of uncountable small nerve proliferation (dozens or hundreds) in the myometrium. All 5 had previously undergone ablation for abnormal uterine bleeding; and all 5 ablations had gone quite deep, focally ablating the inner third of the uterine wall (Figure 2). The purpose of this article is to describe 5 cases of postablation neuromas as the likely cause of pelvic pain, leading to hysterectomy.

2.1 CASE REPORTS

Case 1 - A 47 year old woman had an endometrial ablation in 2007. She also had progressively worsening chronic pelvic pain since 2004, which increased after the ablation, leading to a hysterectomy in 2012. The 40 gm uterus was symmetrical with a 1.4 cm myometrium with no gross lesions or masses. Microscopically, there was no residual endometrium (Figure 3a). Large vessels, markers for the junction of middle and outer third of the wall, were seen close to the surface scar; indicating

that this had been a deep ablation. She had myometrial hyperplasia (MMH) (8,9), a large postablation scar with marked globular elastosis (10), and separate foci of inner myometrial elastosis (Figures 3b,c) as described previously in hysterectomies for pelvic pain (11). S100 immunostains showed innumerable small nerve fibers in the scar tissue on the surface (Figure 3d), far exceeding what is seen in “microneuromas,” and consistent with postablation neuroma.

Case 2 – A 35 year old woman had two prior endometrial biopsies for abnormal bleeding. The first showed secretory endometrium with mild vascular ectasia. The second showed proliferative endometrium with marked vascular ectasia,, the type of pressure effect that has been observed when obstructed venous drainage is caused by fibroids (12). Hysteroscopy has demonstrated spontaneous rupture of such vessels, producing endometrial ecchymoses (13). Similar pressure effects can be due to bulky adenomyosis or bulky MMH (9). Endometrial ablation was then performed for menorrhagia, and the patient soon developed severe pelvic pain and fever that led to 3 readmissions in a month, the last to the intensive care unit with a fever of 104. Milky fluid was aspirated from the endometrial cavity and grew 4+ E. Coli. Clinically, the uterus was presumed to be the source of infection and thus she underwent hysterectomy. At the time of hysterectomy, however, her tubes and ovaries looked normal, with no evidence of pelvic inflammatory disease and no acute endometritis on microscopic exam. Post-ablation tissue necrosis was present, but Brown Hopps stain was negative for bacteria. There was organizing vascular thrombosis of both endometrium and inner myometrium, with subacute inflammation and fibrosis.

The uterus weighed 146 grams postablation, with a 3 cm myometrium (large by historical standards at age 34 but far short of qualifying for designation as myometrial hypertrophy (9,14)). There was focal wall thinning on gross examination, with subtle inward and outward bulges as pressure effects, as illustrated in Figure 2., Endometrial vascular ectasia secondary to pressure effects caused by bulky MMH probably explained the bleeding, as baseline myometrial tone adapted to increased amounts of intramural tissue (9,12,13,15).

As in case 1, the bulky MMH was associated with both pressure effects and inner myometrial elastosis (9,11). Residual endometrium was present. There were no fibroids, nor was there adenomyosis or endometriosis. S100 stain showed markedly increased nerves, far exceeding “microneuromas,” In addition, in this zone of increased small nerves, there was a hyperplastic large nerve visible on H&E (Figure 4), also consistent with a postablation traumatic neuroma.

Case 3 – A 40 year old woman underwent a laparoscopic supracervical hysterectomy for pelvic pain that developed after endometrial ablation. The pieces of uterus weighed 75 grams. There was scant residual endometrium, with a large deep postablation scar with marked globular elastosis (10). S100 stain showed large nerves near the myometrial surface (Figure 5a), indicating that deep ablation had removed the inner third of the wall. Around the large nerves were innumerable smaller nerves, greatly exceeding what is found in microneuromas. In adjacent MMH were innumerable small nerves, diagnostic of postablation neuroma (Figure 5b). There were no fibroids, adenomyosis, or endometriosis.

Case 4 – A 50 year old woman had undergone dilation and curettage for abnormal bleeding in 2008, with the finding of proliferative endometrium. She underwent an ablation in 2010 for continued menorrhagia. In 2012 she had fluid in her endometrial cavity, and was found to have Asherman’s syndrome on hysteroscopy. Repeat D&C showed scant endometrium. A supracervical laparoscopic hysterectomy for pelvic pain and menorrhagia required lysis of adhesions. It yielded 48 grams of morcellated uterine corpus with 2 seedling myomas of 5 mm and 10 mm diameter. There was scant residual endometrium, with vascular ectasia in a postablation scar with marked globular elastosis (10), extending to the surface. These dilated surface vessels were interpreted as the cause of continued bleeding. There was prominent hemosiderosis in the scar. As in previous cases, she had bulky MMH (9), with inner myometrial elastosis (11). There was no adenomyosis or endometriosis, and the seedling myomas were considered insignificant (9). Postablation neuroma was seen on the S100 stain (Figure 6).

Case 5 was a 39 year old woman with a clinical diagnosis of post endometrial ablation syndrome (16). She had undergone an ablation for menorrhagia in 2007 after endometrial biopsy showed secretory endometrium. Despite heavy menses and pelvic pain, preoperative ultrasound showed a small uterus with no fibroids. A hysterectomy was performed

She had a 38 gram uterus, which is small for her age (14), possibly due to the prior deep ablation. Despite scant residual endometrium, endometrial vascular ectasia was still present above the massively elastotic postablation scar. The myometrium was 1 cm thick, with a single 4 mm seedling myoma. Endometrial vascular ectasia, secondary

to bulky MMH with pressure effects, probably explained the bleeding (9,12,13). She had an incidental outer wall perivascular scar (fibrosis uteri), with microneuromas (5,6). An inner wall postablation scar had a most florid example of postablation neuroma (Figure 7). There was no adenomyosis or endometriosis, and a few delicate serosal adhesions were considered insignificant.

3.1 Discussion

This approach to analyzing hysterectomies for benign disease is based on a modern understanding of the uterus as a complex muscular organ with great histologic heterogeneity (8-10); baseline myometrial tone (15,17); contractions during menstrual cycles (18-21); ability to contract both downward and upward towards either cornu (21); perivascular weak points in the wall as seen in the GI tract (22); increased intramural pressure in the presence of bulky MMH, bulky adenomyosis or sizeable fibroids (8,9); and susceptibility to tears in the muscle – analogous to athletic injuries in skeletal muscle - that can lead to elastotic scars in this moving tissue (6,7,10,11) . This concept of highly active, pressure-sensitive, injury-prone myometrium contrasts greatly with a highly prevalent view of quiescent, inactive nonpregnant myometrium that guided pathology interpretations before acquisition of this new knowledge (12,13,15,17-21,23-26).

It is well known to gynecologists and their patients that women with pelvic pain attach a high value to identifying a cause for their pain; but this is often a humbling travail (1). Despite literature suggesting that fibroids, adenomyosis, and endometriosis are not painful per se (2,3,5); standard pathology textbooks do not

yet recommend uterine nerve evaluation in routine practice. We are beginning to believe that such studies have the potential to address the concerns shared by gynecologists and those patients who – after a long, complicated, and expensive ordeal – decide to have a hysterectomy for pelvic pain. We suggest that the present report of objective findings and rational scientific interpretation justifies routine evaluation of small uterine nerves with immunostains to evaluate for postablation neuroma, when pelvic pain increases following an endometrial ablation.

However, it is not yet clear that the same can be said regarding uterine nerve analysis in all hysterectomies for pelvic pain. Clinicopathologic correlation is greatly complicated by the epidemiology of pelvic pain. The Seveso Women’s Health Study suggested that many patients with pelvic pain do not seek medical attention (4). A recent review noted that 41% of women with chronic pelvic pain had not seen a health care provider in the previous year, although 18% had missed work due to pelvic pain (1). We have seen cases with increased inner wall uterine nerves where we did not receive a history of pelvic pain, but were able through additional efforts to obtain such a history. Much better communication between patients, gynecologists and pathologists is needed to address this situation.

Clinicopathologic correlation is further challenged by the pathophysiology of visceral hyperalgesia (1). The test for cutaneous allodynia involves gentle touching of pelvic skin with a cotton swab, sensed by some patients as pain (23). This may reflect a viscerosomatic reflex, whereby the touch signal transmitted to the dorsal paraspinal ganglia is aberrantly relayed to the central nervous system as a pain

signal. A woman who lacks this hyper-reactivity might have objective pathology findings without reporting pain.

A major obstacle to progress has been the lack of a rational scientific explanation for increased inner wall nerves in tissue that appears to be normal by routine H&E stains. We have recently suggested a possible solution (11). In reviewing routine slides of hysterectomies for pain, in conjunction with trichrome and elastic stains, we found a subtle lesion we term inner myometrial elastosis (Figures 3b,c) in at least 50% of cases. It was seen in 3 of the present 5 cases. This may predispose to development of postablation neuromas, although the primary factor appears to be deep ablation that perturbs larger deeper nerves. If inner myometrial elastosis is a reaction to microscopic tears, then nerve proliferation may reflect the action of Nerve Growth Factor in granulation tissue (27). In studies to date, inner myometrial elastosis can be missed if special stains are not done, and if less than 4 sections of myometrium (2 anterior, 2 posterior) are examined.

Inner myometrial elastosis differs from larger elastotic outer wall scars previously reported as fibrosis uteri (Figure 1b)(6). This marker of parity, seldom cited in modern texts despite a literature that goes back over a century (6,7), may reflect healed muscle tears during painful labor contractions. We have seen association of these outer wall scars with microneuromas (Figure 1c). Both tend to occur at perivascular weak points in the wall, analogous to diverticulosis coli (22). Inner myometrial elastosis was probably missed in previous studies because they did not study hysterectomies for pain (24,25). It differs greatly from normal uterine elastic fibers, which are too small to see with elastic van Gieson stains (26). It also

differs from fibrillar elastosis, a more delicate subserosal reaction that tends to be seen in relation to either serosal adhesions, or outer myometrial edema with pressure damage (10). All these elastotic reactions are subtler than the massive globular elastosis that can be seen in post-ablation scars and C-section scars (10).

In conclusion, this appears to be the first report of postablation neuromas in hysterectomies done when pelvic pain increases after a prior ablation for abnormal bleeding. Subtler microneuromas (Figure 1c) have been reported in 30% of multiparous uteri (5), but there is no evidence yet that microneuromas are clinically significant. Our working hypothesis is that they are healing reactions to myometrial trauma during painful labor long before hysterectomy. More study is needed regarding the significance of subtle increases in inner wall nerves (Figure 1a) (2,3,5); with emphasis on obtaining better histories (1,4) and correlation with tests for cutaneous allodynia (23).

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Illustrations

Figure 1a - S100 stain shows increased nerves in inner myometrium, in a routine hysterectomy for otherwise unexplained pelvic pain x200. About a dozen small nerves were seen in this field. They comprise only a tiny fraction of the field, the rest of which serves as an internal negative control; reflecting that large areas of myometrium are routinely completely negative for small nerves, both in our experience and as reported in the literature (5).

Figure 1b – Elastic van Gieson stain of outer wall scar (fibrosis uteri (6)) shows marked globular elastosis (black). The upper left corner and lower left corner are negative for elastic fibers, serving as an internal negative control. Both in the literature, and in our experience, uterine elastic fibers are generally too small to be seen on EVG stains, even when they can be seen on electron microscopy (26).

Figure 1c – S100 stain of microneuroma associated with outer wall scar.

Figure 2 – These 3 slices are all from the same uterus. Deep ablation has focally destroyed the inner third of the uterine wall in the middle (thin) slice. Intact inner third is seen on the right side of the slice on the left (from the anterior wall), and the slice on the right (from the posterior wall). Note the outward bulge of the middle slice with the deep ablation, which is relatively pale due to postablation scar.

Figure 3a - Deep ablation left no residual endometrium in Case 1, so that deep vessels that are markers for the boundary between middle and outer third of the myometrium are near the surface x20.

Figure 3b– Pink amorphous perivascular foci represent inner myometrial elastosis in case 2, as often seen in hysterectomies for pain (11) x400.

Figure 3c - Inner myometrial elastosis is small pale zone on trichrome stain. It is black on elastic van Gieson stain.

Figure 3d - S100 stain of case 1 shows uncountable (dozens to hundreds) small nerve fibers in postablation scar, interpreted as postablation neuroma (compare to Figure 1) x100.

Figure 4- Hyperplastic large nerve that was obvious on H&E in an area of case 2 where S100 stain showed marked small nerve proliferation x100.

Figure 5a - S100 stain of case 3 showed multiple large nerves near the myometrial surface, with innumerable smaller nerves; consistent with postablation neuroma x200.

Figure 5b - S100 stain of case 3 shows more postablation neuroma amidst myometrial hyperplasia x100.

Figure 6 - S100 stain in case 4 showed postablation neuroma in the scar x100.

Figure 7 - Florid postablation neuroma on myometrial surface in case 5. S100 x100.