

Microscopic endometriosis: impact on our understanding of the disease and its surgery

The articles by H. Roman (1) and A. Badescu and H. Roman (2) describing microscopic implants of endometrial glands and stroma located at a distance from deep endometriotic nodules of the bowel are a milestone in the ongoing discussion on the radicality of deep endometriosis excision. They also challenge the concept that “endometrial glands and stroma outside the uterus” define the disease. These articles should be viewed against the background of discussions that took place in the 1980s and early 1990s on microscopic endometriosis (3, 4) and subtle endometriosis (5), in which the three authors of this editorial were actively involved. In addition, we recently discovered that endometrial glands and stroma are frequently found in lymph nodes of women with deep endometriosis.

SHOULD WE REVISE THE DEFINITION OF ENDOMETRIOSIS?

A century ago endometriosis was defined as “endometrial glands and stroma outside the uterus” on the basis of Sampson’s theory of menstrual regurgitation. That “endometrial glands and stroma outside the uterus” constitute pathology is obvious for typical, cystic ovarian and deep endometriotic lesions, because they cause distortion of pelvic organs, adhesions, pain, and/or infertility. However, despite huge research interest, as reflected by more than 29,799 (Scopus) published articles, our understanding of the pathophysiology of endometriosis remains surprisingly poor. Sampson’s theory fails to explain why endometriosis is not found in all women and why, after endometriosis surgery, not all women suffer recurrences while they are still menstruating, considering that retrograde menstruation occurs frequently in most women. Indeed, we have no data documenting the natural history of the disease. We do not understand the hereditary aspects, nor do we comprehend why endometrial tissue injected into the abdominal wall or seeded onto the allantoic membrane of a chicken egg invariably develops into endometriosis-like lesions with invasion and scarring.

Following the description in 1986 that noncolored lesions on the peritoneum, namely subtle vesicles, or polypoid or flame-like lesions, contained endometrial glands and stroma, it was discussed for a decade whether these lesions should be considered to be a pathology, whether they were a cause of pain and/or infertility, and whether they progressed to more severe forms of the disease. Subsequently, the concept of microscopic, or invisible, endometriosis emerged, supported by the observation of microscopic endometriosis in normal-looking peritoneum of women with and without endometriosis (3, 4). Pathology shows these lesions to be very active, and to disappear and reappear in other localizations, but they have never been found to progress to more severe lesions or to cause infertility or pain. However, the opposite is suggested by indirect evidence. Patients diagnosed in the Leuven, Belgium, area with severe endometriosis in the 1990s were not those with subtle or typical endometriosis in the 1980s, and the luteinized

unruptured follicle syndrome is associated with typical lesions but not with subtle lesions. The suggestion that these subtle lesions and particularly microscopic lesions should not be considered to be a pathology was recently reinforced by the observation that endometrial glands and stroma are frequently found in the lymph nodes of women with deep endometriosis without clinical implications. We simply do not know the prevalence of small implants of endometrial glands and stroma on the peritoneum, in lymph nodes, or in the bowel wall of women with and without visible endometriotic lesions.

Clinical evidence strongly suggests that the mere presence of endometrial glands and stroma outside the uterus should no longer be considered to be a clinical pathology by definition. Unfortunately, we cannot distinguish between glands and stroma that have no clinical importance and may disappear spontaneously and those that will develop into endometriosis causing pain and infertility. Hopefully, immunohistochemistry and/or molecular biology one day will allow us to define specific activities or processes causing the endometriosis pathology and therefore to distinguish between normal and pathologic “endometrial-like tissue outside the uterus.”

ENDOMETRIOSIS SURGERY AND ERADICATION OF ALL ENDOMETRIAL CELLS AND STROMA

As discussed in both current articles (1, 2), the concept that endometriosis surgery should eradicate all disease to prevent recurrence has resulted in increasing use of bowel resections instead of more conservative excision of deep endometriosis. Indeed, the multifocality of deep endometriosis and the fact that some resection margins were not free of endometriosis in 8%–20% of cases were considered to be arguments in favor of an even more radical approach.

These articles nicely document that foci of endometrial glands and stroma are a frequent phenomenon in deep endometriotic nodules of the bowel, and their incidence decreases exponentially with distance from the nodule ≥ 5 cm. It is also demonstrated that short-term clinical outcomes are not different between women with and without small endometrial cell nests in their resection margins.

A first obvious conclusion is that endometrial glands and stroma in the resection margins are probably much more common than previously thought. Indeed, it is logical to assume that many more nests will be found by serial sections of the margins. In addition, an absence of “endometriosis-free resection margins” does not mean that no endometrial cells remain in the bowel. This and similar clinical outcomes in women with and without “endometriosis-free resection margins” is, moreover, consistent with the observation that recurrence rates of deep endometriotic nodules in the bowel are low after both bowel resection and conservative excision.

CONCLUSION

A tentative conclusion might be that the occurrence of small, macroscopically invisible, nests of endometrial glands and

stroma is much more frequent than we thought on the peritoneum, in pelvic lymph nodes, and inside the bowel walls, at least in women with endometriosis. It is also strongly suggested that most of these endometrial cell nests do not constitute a clinical pathology or develop into more severe lesions, nor do they cause pain or infertility.

We clearly do not have all the answers today. However, when performing surgery, we have to decide one way or another: a conservative approach or radical bowel resection. Both of the current articles have the merit of stimulating our thinking about endometriosis pathophysiology and guiding our surgical strategy. We have solid arguments both for a more radical approach to eliminate as many endometrial cells and stroma as possible as well as for a less radical approach leaving a rim of fibrosis obviously containing some endometrial cells. Recurrence rates of pain and of endometriotic nodules will be the final judge in determining the most suitable therapy. These recurrence rates will also be important for expanding our knowledge of the natural history of small nests of endometrial glands and stroma outside the uterus, and hopefully our understanding of when, why, and how these endometrial cells turn into a pathology with clinical implications.

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