

# Lymph node involvement and lymphovascular invasion in deep infiltrating rectosigmoid endometriosis

Jean-Christophe Noël, M.D.,<sup>a</sup> Charles Chapron, M.D.,<sup>b</sup> Isabelle Fayt, M.D.,<sup>a</sup> and Vincent Anaf, M.D.<sup>c</sup>

<sup>a</sup> Department of Pathology, Erasme University Hospital, Free University of Brussels, Brussels, Belgium; <sup>b</sup> Department of Gynecology, CHU Cochin-Saint Vincent de Paul, Université Paris V, Paris, France; and <sup>c</sup> Department of Gynecology, Erasme University Hospital, Free University of Brussels, Brussels, Belgium

**Objective:** To analyze the lymph node involvement by endometriotic foci in rectosigmoid endometriosis and to correlate it with clinical and histological parameters including the presence of lymphovascular invasions, which could explain this lymph node involvement.

**Design:** A prospective study of 26 consecutive cases of rectosigmoid endometriosis between January 2005 and January 2007.

**Setting:** A multidisciplinary study including clinical and pathological data.

**Patient(s):** Twenty-six patients with symptomatic rectosigmoid endometriosis.

**Intervention(s):** Laparoscopic surgery with pathological analysis of each specimen.

**Main Outcome Measure(s):** Involvement of lymph nodes by endometriotic foci was correlated with the size and the wall layers affected by endometriotic lesions, the number of lymph nodes retrieved, and the presence of lymphovascular invasions demonstrated by D2-40, a specific antibody to lymphatic vessels.

**Result(s):** Lymph node involvement by endometriosis was observed in 11 of the 26 patients (42.3%) and correlated with the size of the lesions, the number of lymph nodes retrieved, and the presence of lymphovascular invasions, which were observed in 36.3% of cases.

**Conclusion(s):** Our data confirm that lymph node involvement by endometriotic foci is a frequent event in rectosigmoid endometriosis and may result at least partially from a lymphatic spread of the disease. (Fertil Steril® 2008;89:1069–72. ©2008 by American Society for Reproductive Medicine.)

**Key Words:** Endometriosis, bowel, rectosigmoid, lymph node, lymphatic vessel, vascular invasion, D2-40

Endometriosis is defined by the presence of glands lined by endometrial-type epithelium surrounded by endometrial stroma outside the uterine endometrial mucosa and myometrium (1). This pathology occurs most frequently in women of childbearing age and can be located in various anatomic sites including the peritoneum, ovary, fallopian tubes, cervix, vagina, vulva, rectovaginal septum, uterosacral ligaments, rectosigmoid bowel, bladder and ureters, and skin (1, 2). Lymph node involvement by endometriosis is considered to be uncommon, and the status of lymph nodes in endometriosis remains obscure because evidently lymph node dissection is usually not performed for a so-called benign disease. One exception is probably rectosigmoid endometriosis, where the regional lymph nodes present in the mesocolon are easily accessible (3).

Therefore, to clarify the issue, we have studied surgical resections for rectosigmoid endometriosis, with the lymph node involvement by “real” endometriotic foci strictly defined by the presence of glands and stroma. Others forms of Müllerian abnormalities unaccompanied by stroma including benign Müllerian cysts (Müllerian glands lined by nonciliated epithelium) or endosalpingiosis (Müllerian glands lined

by a ciliated tubal epithelium), which are frequently confused in the literature with endometriosis, were excluded (4–7).

In addition, to verify the hypothesis that lymph node involvement may result from a vascular drainage, the possible lymphovascular invasions by glands and/or stroma in rectosigmoid endometriosis have been assessed using immunohistochemistry with the D2-40 antibody. D2-40 has been shown to react with the glycosylated and nonglycosylated epitopes of gp36 and is identical to podoplanin. D2-40 has been shown to be a sensitive marker for lymph vessel endothelium, which has been widely used to identify lymphovascular invasion in primary carcinomas of the breast, colon, prostate, cervix, and endometrium (8–10).

## MATERIALS AND METHODS

Twenty-six cases of rectosigmoid resections were prospectively studied in the Gynecopathology Department of Erasme University Hospital, Brussels, between January 2005 and January 2007. Subjects were nonmenopausal women who were not currently on hormone treatment and who had stopped hormone treatment for  $\geq 2$  months. No patient had undergone previous bowel surgery. Only consenting patients were included in the study, which was approved by the local institutional ethics committee.

The mean age of the 26 patients was 32 years, the length of the resected bowel was 16.4 cm, and the size of the

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Reprint requests: Jean-Christophe Noël, M.D., Service d'Anatomie Pathologique, Hôpital Universitaire Erasme, 808 Route de Lennik, 1070 Brussels, Belgium (FAX: 25554790; E-mail: jenoel@ulb.ac.be).

endometriotic lesions 28.5 mm. The surgical technique used for large bowel resection was identical in all cases and was performed by the same investigator (VA). Three conditions were required for the choice of the place of proximal and distal large bowel division. First, the large bowel was divided so that the resulting area was free of any induration at peroperative manual palpation; second, it was divided so that the resulting area was free of any serosal or muscular endometriotic implant; and third, with the help of a graduated scale, it was divided at a distance of at least 3 cm from the edges of the palpated lesion.

For each patient, the whole mesocolon was resected during the procedure. The mesocolon was cut perpendicularly to the axis of the resected colon until the point of its posterior attachments at the level of the sacrum or promontorium and then cut at the level of the sacral concavity. Thus, a lymphadenectomy was performed in all cases.

A mean of six lymph nodes were found for each patient, and the range was 3–13 lymph nodes retrieved. Five histological sections of each lymph node were performed and stained with hematoxylin-eosin.

The immunohistochemical demonstration of lymphovascular invasion was assessed by D2-40 antibody. In brief, 4- $\mu$ m paraffin sections were placed on silanized slides, dewaxed in xylene, and rehydrated in decreasing concentrations of ethanol. While immersed in a modified citrate buffer (pH 6.1; S1700-Dako, Glostrup, Denmark), slides were placed in a calibrated warm water bath (95–99°C) for 60 minutes for epitope retrieval. Tissues were then incubated for 1 hour at room temperature with the primary antibodies D2-40 (clone D2-40, dilution 1/50, Dako). The Ultra Vision Labeled Polymer (Lab Vision, Fremont, CA) was used for the subsequent steps according to the manufacturer's instructions. Chromogenic development was accomplished using diaminobenzidine-hydrogen peroxide. Slides were then slightly counterstained with hematoxylin and dehydrated, and coverslips were applied. To control for nonspecific binding, as negative controls, the primary antibody was substituted in the first layer of the serial sections.

The presence or absence of lymph node involvement was analyzed in relation to other parameters: age, size of the lesions, deepest layer of bowel wall affected, number of lymph nodes retrieved, and presence of lymphovascular invasion. The pathological analysis was carried out by the same investigator (JCN).

Comparison of the data was performed using Student's *t*-test and the Mann-Whitney test for quantitative variables depending on the normal distribution of data and the  $\chi^2$  test for categorical variables.  $P < .05$  was considered statistically significant.

## RESULTS

Lymph node involvement by endometriosis was observed in 11 (42.3%) of the 26 patients, with one to a maximum of four

lymph nodes affected. The endometriotic foci were located in the capsule or cortical area or were characterized by a more central location within the node. Some of the stromal elements exhibited decidual reaction (Fig. 1). Rupture of the lymph node capsule was observed in rare cases.

The lymph node–positive status correlated significantly with the number of retrieved lymph nodes ( $P < .05$ ) and the size of the lesions but not with the age or deepest layer of the bowel wall affected by endometriosis ( $P = \text{NS}$ ; Table 1). Lymphovascular invasion consisting of cytogenic stroma or glands and stroma was observed in four (36.3%) of the 11 patients with lymph node involvement and in two (13.3%) of the 15 patients without lymph node involvement ( $P < .05$ ; Table 1 and Fig. 1).

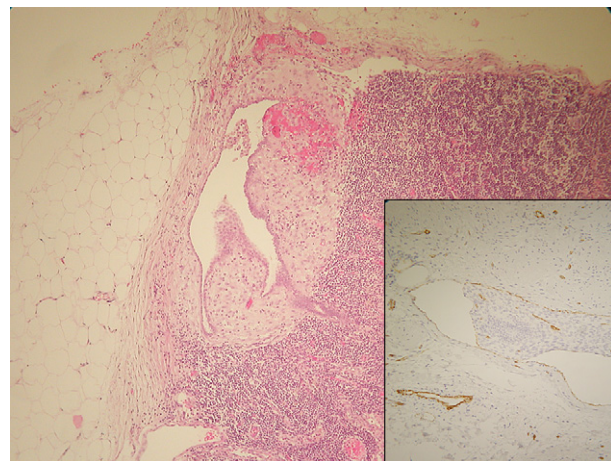
## DISCUSSION

Lymph node involvement by endometriosis is considered to be uncommon, and the majority of examples reported as such are lymph nodes with involvement by other benign endometrial stroma that are devoid of Müllerian abnormalities including Müllerian cysts or endosalpingiosis. The frequency of the latter varied from 2% to 41%, and the cases are almost always incidental microscopic findings that are found in association with peritoneal endosalpingiosis, salpingitis, ovarian borderline serous tumors, or carcinomas (4–7).

In the present study, we have clearly demonstrated that lymph node involvement by endometriosis is a frequent occurrence and is found in 42.3% of the lymph nodes retrieved in the mesocolon of rectosigmoid resections for extensive and

**FIGURE 1**

Endometriotic foci in lymph node. Note the decidualization of the stroma. (Inset) Lymphovascular invasion by endometriotic foci in corresponding rectosigmoid endometriosis. Positive staining of the endothelium is outlined with D2-40 antibody (hematoxylin-eosin  $\times 20$ ).



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