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Research Letter

A rare case of endometriosis in Turner's syndrome

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Endometriosis is defined by the presence of functional endometrial tissue outside the uterine cavity and musculature. It has a prevalence rate as high as 35–50% in women experiencing pain or infertility [1] and sometimes has a peculiar and rare onset [2,3].

Endometriosis is a common disease in menstruating women [4,5] but has also been reported in postmenopausal or surgically castrated women on hormone replacement therapy (HRT) [6]. The common denominator of all such cases is exposure to female hormones [7]. However, endometriosis, a common and important clinical problem in women of reproductive age, has rarely been described in prepubertal girls. In patients with Turner's syndrome or other ovarian dysgenesis, endometriosis is very rare. Some cases are subclinical, and endometriosis is an incidental finding during routine examination. Although endometriosis was described in the medical literature at the end of the 19th century, and the first theories regarding its hystogenesis were developed at the beginning of the 20th century, the real pathogenesis of endometriosis remains unknown. Most studies about the etiology of endometriosis claim that the main possible causes of endometriosis are probably multifactorial. Three theories of histogenesis have been proposed. (1) The metastatic theory [8] proposes the transplantation of endometrial tissue via retrograde menstrual implantation, vascular/lymphatic spread, and intraoperative implantation. (2) The coelomic metaplastic theory [9] suggests that the germinal epithelium of the ovary can be transformed by metaplasia into endometrium. This theory, which initially explained only ovarian endometriosis, has since been extended to the peritoneal serosa, as embryologic studies have indicated that Müllerian ducts, the germinal epithelium of the ovary, and the pelvic peritoneum are all derived from the same embryologic precursor [10]. (3) The induction theory [4] combines the first two theories and suggests that substances released from exfoliated endometrium induce the formation of endometriotic tissue in undifferentiated mesenchymal cells. In addition, researchers are currently investigating the role of growth factors, immunity, and other mechanisms that may contribute to the development of this disorder.

We report a rare case of endometriosis on the peritoneum of a Turner's syndrome patient, in which we demonstrate the presence of vestigial Müllerian remnant tissue at the peritoneal site, initiating the growth of ectopic endometrial tissue.

A 22-year-old woman was admitted to our department for menstrual abnormalities (hypomenorrhea and intermittent spotting). She came to us with an interesting clinical history. At 30 days after birth, she was diagnosed with an intraductal aortic coarctation and patent ductus arteriosus, for which she required surgery. Since then, she had undergone several clinical examinations to detect possible anomalies. At the age of 11 years, doctors requested a cytogenetic examination of her lymphocytes, and mosaic Turner's syndrome was diagnosed. The pediatrician's attention was drawn to the girl's characteristics of Turner stigmata, a low posterior hairline, webbing on the neck, short fourth and fifth metatarsals, moderate scoliosis, and a central pattern of fat distribution. In the same year, elevated blood pressure was found: systolic 161 mmHg and diastolic 113 mmHg. Therapy with atenolol was started as a result. At the age of 18 years she was diagnosed with hypothyroidism, requiring therapy with L-thyroxine. At her most recent visits in April 2011, the asymptomatic patient had been taking atenolol (100 mg twice a day) and L-thyroxine (100 μg daily) along with HRT with estrogen and progestogens.

On physical examination, she was 150 cm tall and weighed 56 kg (body mass index, 24.9 kg/m^2). Her initial blood pressure was 125/65 mmHg. Her breasts were small and undeveloped and were assessed to be at Tanner stage 2. Pubic hair was scarce. On pelvic examination, the length of the vagina was found to be normal at 8 cm, and a normal uterus was palpated. The measurement of peripheral gonadotropins revealed the follicle-stimulating hormone level to be > 30.7 mIU/mL and luteinizing hormone level to be 4.8 mIU/mL. On pelvic ultrasound, the anteverted and anteflexed

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uterus were normal in size, the myometrial echo pattern was slightly uneven, and a corpuscular cystic mass was visible on the right-hand side, measuring about 8 cm × 5 cm.

Computed tomography and magnetic resonance imaging were performed after a 6 cm × 4 cm neoformation was found.

Magnetic resonance imaging with T1- and T2-weighted sequences in axial (Fig. 1), sagittal (Fig. 2), and coronal planes, with fat suppression and injection of intravenous contrast medium, showed the following: a myometrial structure with slightly uneven intensity plus small nabothian cysts between the body and neck; a cystic mass of about 9 cm × 5 cm in the pouch of Douglas with some internal branching and a solid small disk of tissue in the wall of the right anterolateral portion. This "token" of tissue showed net enhancement of contrast medium and was inseparable from the right ureter tract preterminal, determining dilation upstream. The findings were compatible with a heteroplastic injury. Another two masses, contiguous and with similar characteristics, measuring about 6 cm × 4 cm and 2.5 cm × 1.5 cm, respectively, were apparent on the left adnexal, but without solid "token" in the wall. The specimen's characteristics and signal impregnation, with contrast set to medium, were consistent with mucinous adenocarcinoma. Computed tomography did not provide any additional information.

The diagnostic radiological findings prompted laparoscopy.

During the laparoscopy, a pelvic mass was evident. The mass had a smooth surface and was tenaciously adherent to the rectosigmoid colon and to the front surface of the bladder.

Because there were many adhesions, the procedure was converted to laparotomy.

During the surgery, opening the retroperitoneal space revealed the ureters. The right ureter was expanded to the junction with the uterine artery. For this reason, it was mobilized and the mass was excised. There were no clear signs of malignancy, but endometriosis was suspected. An extemporaneous examination was performed.

The pathologist's final report revealed that the first mass, which was removed, contained a smooth wall exteriorly with endometrial glands and stroma lining the interior of the cyst with abundant hemosiderin-laden macrophages, consistent with an endometrioma (Fig. 3). Vestigial Müllerian remnant tissue was visible close to the endometriosis hearth (Fig. 3, inset), which, under hormonal stimulation, started ectopic mass growth. The other masses were serous cystadenomas.

Endometriosis is a common disorder in fertile women, but some studies have reported anomalous cases of endometriosis in postmenopausal women with HRT [11], in men with prostate cancer with hormonal therapy [12], in women with ovarian dysgenesis

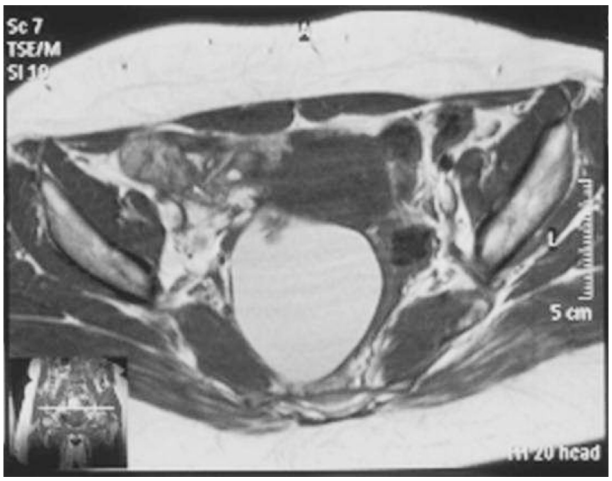

Fig.1. Magnetic resonance imaging with T1-weighted sequences in axial view.

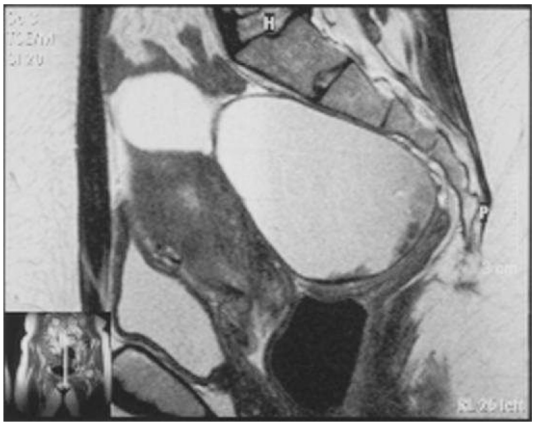

Fig. 2. Magnetic resonance imaging with T2-weighted sequences in sagittal view.

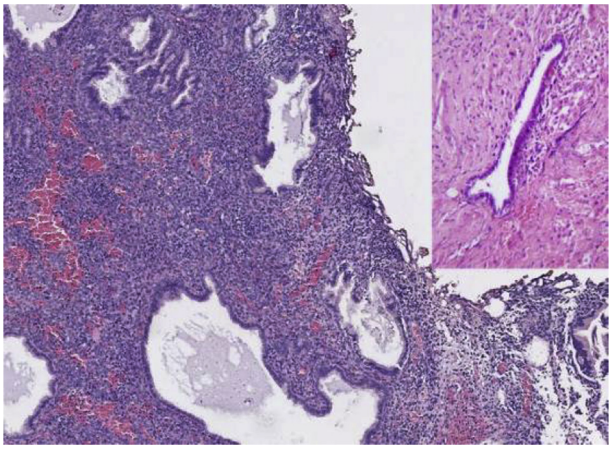

Fig. 3. Typical endometrial glands surrounded by stroma and bordered by vessels with occasional foci of hemosiderin-laden macrophages, typical of endometriosis (hematoxylin and eosin stain, ×10). Inset: Müllerian remnant tissue close to endometrial implant in the peritoneal cavity (hematoxylin and eosin stain, ×10).

[13], and in Turner's syndrome patients with HRT. Although such patients have hormonal therapy in common, there have been a few exceptional cases in which endometriosis had developed although there was no influence of exogenous hormones. Among these was a case of an 8-year-old girl with premenarcheal endometriosis described by Marsh and Laufer [14], and in 2006 Lazovic et al [15] reported a 27-year-old woman with Turner's syndrome without a uterus or ovaries that was not treated with hormonal replacement. Finally, another case of endometriosis in a Turner's syndrome patient without HRT was described by Kourounis et al in 2004 [16]. The question is, "why do some patients who are using HRT develop endometriosis whereas others do not?"

Although there are different hypotheses on the etiology of endometriosis, we support and demonstrate the metaplastic theory with our case and associated pathological examinations.

Following HRT therapy, our patient was having scanty menstrual flows (hypomenorrhea) and intermittent spotting. This intermittent spotting meant that we could not exclude the metastatic theory; however, the presence of Müllerian tissue close to the endometriotic lesion provided decisive proof for the metaplastic theory.

The theory of histogenesis describes metaplastic differentiation of serosal surfaces (coelomic epithelium) or Müllerian remnant tissue. Both endometrial and peritoneal cells derive from the coelomic wall—epithelium. The theory suggests the possibility of

peritoneal cell differentiation into functioning endometrial cells, under hormonal stimulation.

Our patient conforms with this theory because the pathological examination allowed us to demonstrate the existence of Müllerian remnant tissue as mentioned above.

Among the cases in the literature, some confirm our hypothesis, whereas others seem to refute it.

The influence of hormonal therapy on the development of endometriosis in Turner's syndrome patients seems evident in the cases reported by Binns et al [17], Bösze et al [18], Meinen et al [19], and Tazuke and Milki [20]. Their patients had been subjected for some time to HRT prior to the diagnosis of endometriosis. This therapy was intended to allow the development of secondary sexual characteristics and normal growth.

It is likely that the altered hormonal profiles contributed to the development of endometriotic implants; it is also likely that these implants originated from metaplastic differentiation of serosal surfaces or Müllerian remnant tissue.

The influence of hormonal therapy on the development of endometriosis is also evident in cases of postmenopausal women with HRT and in cases of men in hormonal therapy for the treatment of prostate cancer. The correlation between HRT and metaplastic differentiation of Müllerian remnant tissue as an etiopathogenetic mechanism of endometriosis is, in these circumstances, much more probable.

The cases described by Doty et al [21] and Peress et al [22] reported treatment with HRT but refuted the theory of retrograde menstruation as the pathogenesis of endometriosis: the former reported the case of a woman with persistent amenorrhea despite treatment, and the latter reported an endometrial biopsy following HRT that revealed atrophic endometrial glands and stroma.

Like the current case, they did, however, support coelomic metaplasia as the mechanism of pathogenesis of endometriosis in Turner's syndrome.

Regarding cases that seem to refute our theory, the following considerations should be taken into account.

First, Lazovic et al's [15] case began hormonal therapy after explorative laparoscopy, rather than prior to the development of endometriosis.

It is likely that endometriotic implants, defined as “hardly noticeable”, need to proliferate in ectopic endometrial tissue. Therefore, they were not obvious previously because they had not been subjected to HRT.

Kourounis et al [16] described a case of Turner's syndrome with endometriosis and a history of replacement therapy with growth hormones and androgens without hormonal therapy. It is likely that these hormones altered the full hormonal profile. This theory is supported by some authors [23].

Kourounis et al [16] also state that endometriosis cannot be explained on the basis of the implantation theory. In this case report, the appearance of endometriosis could be attributed to the transformation of the coelomic epithelium into endometrial glands, as a result of unspecified stimuli.

Our case provides support for the metaplastic theory of endometriosis. Fundamental support was provided by pathological examinations in which Müllerian remnant tissue was identified near the endometrial implant in the peritoneal cavity. However, further studies are required to confirm our theory.

Our clinical case also provides a small piece of the puzzle for understanding the complex pathology of endometriosis, the pathogenesis of which remains unclear. As for any other pathology, an overall understanding of its causes and pathogenesis is the first step toward improving the clinical approach: only with in-depth knowledge will it be possible to develop specific preventative and therapeutic approaches to treat this condition.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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