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ARTICLE

New evidence of the presence of endometriosis in the human fetus

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Pietro Signorile is a pioneer of modern advanced laparoscopic surgery, with more than 20 years' experience in clinic, surgery and research in endometriosis. He is Director of the Italian Endometriosis Center, a multidisciplinary center for diagnosis and treatment of endometriosis, and President of the Italian Endometriosis Foundation, established in 2007 and fully dedicated to translational research in endometriosis, through an international network of research programs and scientists.

Abstract The aetiology of endometriosis, a gynaecological disease defined by the histological presence of endometrial glands and stroma outside the uterine cavity, is still open to debate. Research has recently found evidence for endometriosis in human female fetuses at different gestational ages. This paper reports a new case of fetal endometriosis in a 25-week female fetus, deceased due to placental pathology, from a series of 13 female fetuses analysed at autopsy. The exact anatomical localization of this misplaced endometrium, as well as its histopathological and immunohistochemical characteristics are illustrated. The case suggests that endometriosis can be caused by dislocation of primitive endometrial tissue outside the uterine cavity during organogenesis.

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Introduction

Endometriosis is classically defined as the growth of endometrial glands and stroma at extrauterine sites, most commonly implanted over visceral and peritoneal surfaces within the female pelvis (Baldi et al., 2008; Giudice and Kao, 2004). It is a prevalent gynaecological disorder that may be present in 10% of women of reproductive age (Wheeler, 1992). Deep infiltrating endometriosis is a particular form of endometriosis associated with pelvic pain symptoms, located under the peritoneal surface (Koninckx and Martin, 1994; Signorile et al., 2009a). Endometriosis is often accompanied by chronic pelvic pain, adhesion formation and infertility and is responsible for more than 100,000

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hysterectomies each year in the USA alone, with the annual healthcare costs attributable to this disease of over US$ 1 billion (Carlson et al., 1994). Although there are several theories, research scientists remain unsure as to the definitive cause of endometriosis. The most commonly accepted mechanism for the development of peritoneal endometriotic lesions is Sampson's theory, claiming that the endometrial debris in retrograde menstruation implants, survives and grows in the peritoneal cavity (Sampson, 1927a). On the other hand, the coelomic metaplasia hypothesis proposes that genesis of endometriotic lesions within the peritoneal cavity is caused by the differentiation of the original coelomic membrane into endometrium-like tissue (Brosens, 2004; Nap et al., 2004; Nisolle and Donnez, 1997). A third hypothesis claims that menstrual tissue from the endometrial cavity is able to migrate to other sites through veins or lymphatic vessels (Sampson, 1927b). Recently, the possibility that circulating stem cells originating from bone marrow could differentiate into endometriotic tissue at different anatomical sites has also been also proposed (Sasson and Taylor, 2008). As a matter of fact, proving or disproving all these hypotheses is difficult, since there are no or few suitable in-vitro or in-vivo models.

Interestingly, a different theory, formulated by pioneer scientists of this disease in the late 17th and 18th centuries, postulates that endometriosis is caused by small defects of embryogenesis (Benagiano and Brosens, 2006; Knapp, 1999). Lately, this theory has been taken up again and named either Mülleriosis or Müllerianosis (Batt and Smith, 1989; Batt et al., 2007; Redwine, 1987). The presence of ectopic endometrium has recently been demonstrated in 11% of human fetuses analysed during autopsy (Signorile et al., 2009b). This is a report of a new case of endometriosis in a female fetus of 25 weeks of gestation, found among a series of 13 female fetuses analysed at autopsy. Detailed histological and immunohistochemical characterization of the fetal ectopic endometrium showed that it displays a phenotype exactly alike to that of the fetal endometrium. The aetiopathological and clinical implications of this observation are discussed.

Materials and methods

A series of 13 human female fetuses that died at different times of gestation (from 25 weeks to newborn) were collected at autopsy. A single case of fetal endometriosis was found in a human female fetus at the gestational age of 25 weeks, deceased owing to placental pathology. Anatomopathological examination of the fetus did not display any visible alteration of the pelvic organs. Pelvic organs were collected en block, fixed in paraformaldehyde, embedded in paraffin wax and histologically analysed using haematoxylin/eosin and haematoxylin/Van Gieson staining. For immunohistochemistry, 5–7 μm specimen sections embedded in paraffin, were cut, mounted on glass and dried overnight at 37°C. All sections were then deparaffinized in xylene, rehydrated through a graded alcohol series and washed in phosphate-buffered saline (PBS). PBS was used for all subsequent washes and for antiserum dilution. Tissue sections were quenched sequentially in 3% hydrogen peroxide in aqueous solution and blocked with PBS-6% non-fat dry milk (Biorad, Hercules, CA, USA) for 1 h at room temperature. Slides were then incubated at 4°C overnight at 1:100 dilution with the following antibodies: the affinity-purified rabbit antibody ERα for the oestrogen receptor (sc-542; Santa Cruz, Santa Cruz, CA, USA), the mouse monoclonal antibodies for CA125 (clone M11), vimentin (clone V9), for desmin (clone D33), CD10 (clone M7308) and cytokeratin 7 (clone OV-TL 12/30) (Dako Laboratories, Carpinteria, CA, USA). After three washes in PBS to remove the excess of antiserum, the slides were incubated with diluted goat anti-rabbit or anti-mouse biotinylated antibodies (Vector Laboratories, Burlingame, CA, USA) at 1:200 dilution in PBS/3% non-fat dry milk (Biorad, Milan, Italy) for 1 h. All

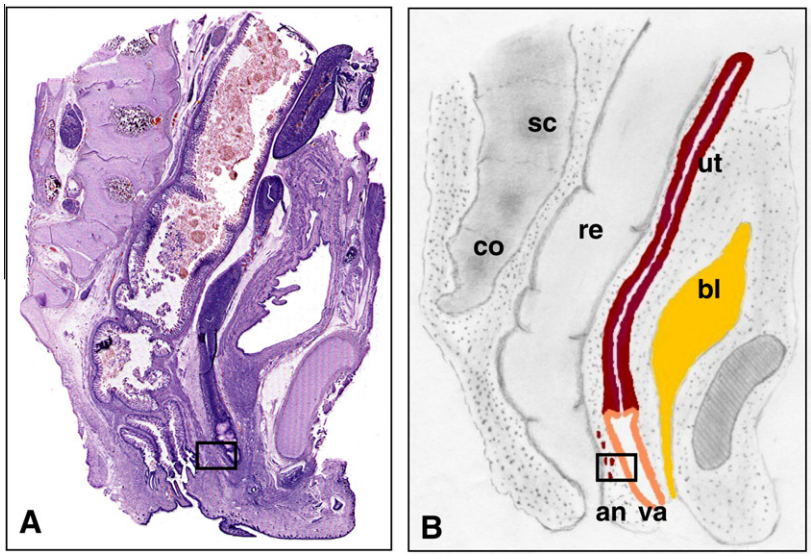

Figure 1 Anatomical distribution of the ectopic endometrium in a female human fetus of 25 weeks of gestation. (**A**) The small rectangle indicates the exact anatomical location of the endometriotic structures deep in the rectovaginal septum. (**B**) A schematic representation of the fetus, displaying the anatomical relationship between the organs and the endometriotic structures, indicated by the small rectangle (×1). an = anus; bl = bladder; co = coccyx; re = rectum; sc = spinal column; ut = uterus; va = vagina.

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