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ARTICLE

New evidence of the presence of endometriosis in the human fetus

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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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KEYWORDS: CA125, CD10, cytokeratin 7, endometriosis, fetus, Mülleriosis, oestrogen receptor

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

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 μ m 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 ER α 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

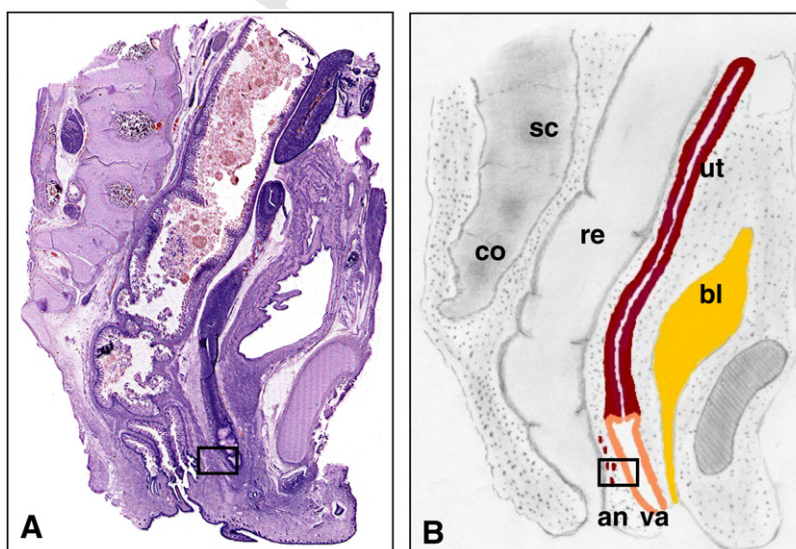


Figure 1 Anatomical distribution of the ectopic endometrium in a female human fetus of 25 weeks of gestation. (A) The small rectangle indicates the exact anatomical location of the endometriotic structures deep in the rectovaginal septum. (B) A schematic representation of the fetus, displaying the anatomical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

the slides were then processed by the ABC method (Vector Laboratories) for 30 min at room temperature. Diaminobenzidine (Vector Laboratories) was used as the final chromogen and haematoxylin was used as the nuclear counterstaining. Negative controls for each tissue section were prepared by leaving out the primary antiserum. Positive controls of breast, intestinal and uterine tumour tissues expressing each of the antigens analysed, were run at the same time. All samples were processed under the same conditions. Experiments were performed in compliance with the Helsinki Declaration and the protocols were approved by the ethics committee of the Italian Endometriosis Foundation.

Results

Pelvic organs were analysed in their entirety. To this end, four sections were taken every 150 μ m and stained for histology and for immunohistochemistry, as described in the methods section. No evidence was found of macroscopic or microscopic defects of the genital system in the fetus

analysed (data not shown). Concerning the selection of the immunohistochemical markers, ER α is known to be expressed in the luminal epithelium of the endometrium and subepithelial stroma during fetal life (Markey et al., 2005), CA125 and cytokeratin 7 are well established markers of the gynaecological tract (Nap, 1998; Scharl et al., 1989; Vang et al., 2001), while CD10 is expressed in the stromal cells of endometriosis (Groisman and Meir, 2003; Sumathi and McCluggage, 2002). On the other hand, vimentin and desmin are specific markers of connective and muscular tissues (Rubin and Farber, 1994).

Indeed, in the rectovaginal septum, the presence of organoid structures outside the uterine cavity were found, clearly resembling the structure of the primitive endometrium and expressing CA125, cytokeratin 7 and oestrogen receptor in the epithelial component. The stromal cells expressed both CD10 and the oestrogen receptor. These glandular structures were dislocated outside the uterus and could not be ascribed to any normal anatomical formation. The exact anatomical distributions of these glandular structures are depicted in Figure 1. To note,

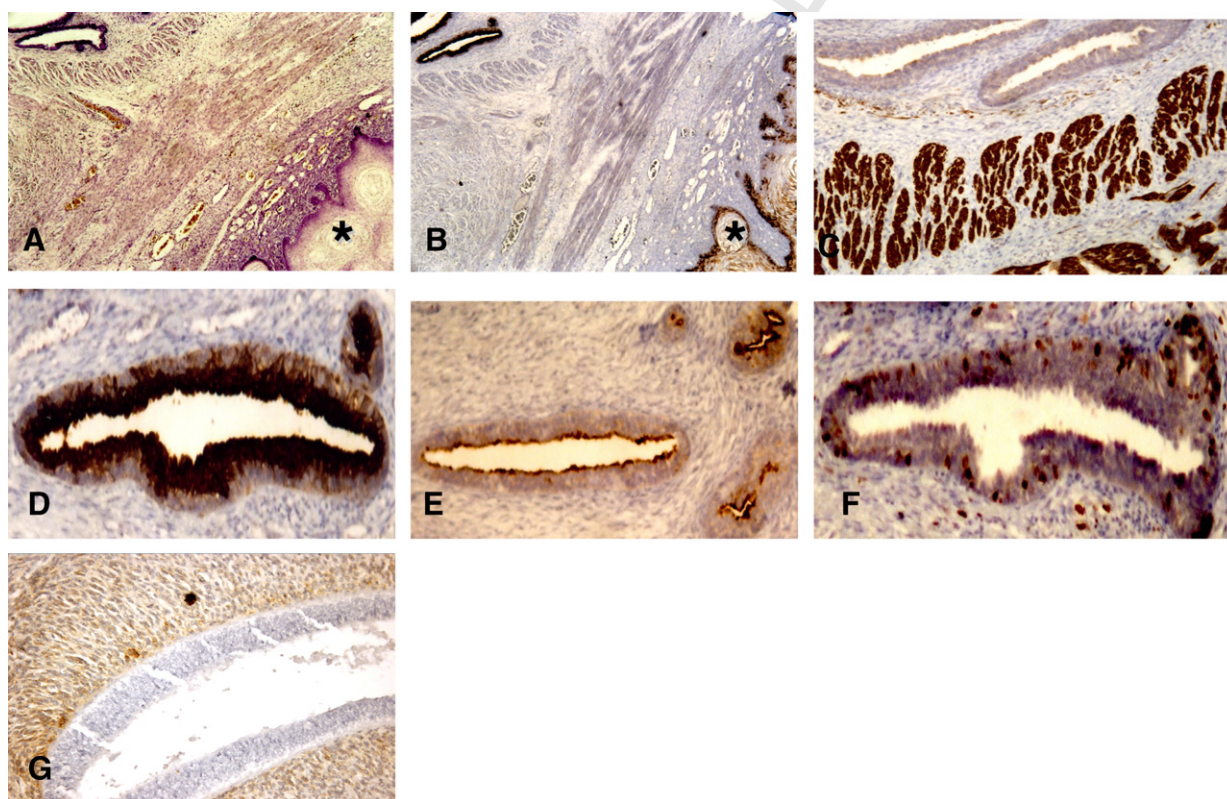


Figure 2 Histological and immunohistochemical appearance of ectopic endometrium. (A) Histological appearance of the endometriotic glands, visible in the upper left corner of the picture; the vagina is indicated by an asterisk (the area visible corresponds to the one delineated by the rectangle in Figure 1A and B; haematoxylin and eosin, original magnification $\times 10$). (B) Strong immunohistochemical expression of cytokeratin 7 in the endometriotic structures. Note that the epithelium of the vagina (indicated by an asterisk) is also positive for cytokeratin 7 (ABC, original magnification $\times 10$). (C) Negative immunohistochemical expression for desmin of the endometriotic structure; note that the muscle tissue is strongly positive for desmin (ABC, original magnification $\times 20$). (D) One of the glandular structures displaying strong immunohistochemical expression for cytokeratin 7 (ABC, original magnification $\times 40$). (E) One of the glandular structures displaying strong immunohistochemical expression for CA125 (ABC, original magnification $\times 40$). (F) One of the glandular structures displaying strong immunohistochemical expression for oestrogen receptor; several stromal cells also expressed oestrogen receptor (ABC, original magnification $\times 40$). (G) One of the glandular structures displaying strong immunohistochemical expression for CD10 in the stromal cells surrounding the epithelial component (ABC, original magnification $\times 40$).

the rectovaginal septum is a common location for deep endometriosis in women (Rubin and Farber, 1994). The histological and immunohistochemical appearances of these structures are depicted in detail in Figure 2. Interestingly, the identical expression pattern for the molecular markers analysed, was detected for the endometrium inside the uterine cavity, as depicted in Figure 3. Nevertheless, the absence of goblet cells and the immunohistochemical phenotype exclude the hypothesis that these structures could be rectal glands. These structures must be ascribed to endometrial tissue, misplaced outside the uterine cavity during the earlier steps of organogenesis and displaying identical molecular phenotype to the endometrium present in the uterus.

Discussion

Sampson's theory of reflux menstruation is still the most popular and accepted pathogenetic mechanism for endometriosis. Endometriosis, would, therefore, represent simply an autotransplant, in which normal endometrial tissue is transplanted to an ectopic location in the organism. Despite the fact that this theory is considered by the majority of scientists involved in endometriosis research as a hypothesis, several clinical and experimental data contrast this idea. First of all, retrograde flow is a very common condition

affecting the great majority of women, but less than 15% of women develop endometriosis (Bulun, 2009). Furthermore, it has been shown that endometrial cells are not commonly present in peritoneal fluid (Batt and Mitwally, 2003; Redwine, 2002, 2003). Moreover, the presence of the disease in early puberty and exceptionally also in newborns (Batt and Mitwally, 2003; Diez Garcia et al., 1996; Ebert et al., 2009; Marsh and Laufer, 2005), as well as in women affected by the Mayer–Rokitansky–Küster–Hauser, a syndrome characterized by congenital aplasia of the uterus and the upper part of the vagina (Balci et al., 2008; Enatsu et al., 2000; Yan and Mok, 2002), further contrast the validity of the theory. However, it should be noted that some researchers have demonstrated the presence of uterine remnants, capable of retrograde menstruation in a patient with Mayer–Rokitansky–Küster–Hauser and pelvic endometriosis (Parker and Kamau, 2009). Nevertheless, elegant observations by Redwine (2002) strongly suggest that endometriotic tissue lacks the characteristics of an autotransplant. Moreover, this theory fails to explain the presence of endometriosis in such remote areas as the lungs, skin, lymph nodes and breasts (Baldi et al., 2008; Bulun, 2009). Finally, proponents of Sampson's theory have never been able to demonstrate *in vivo* the attachment of menstrual endometrium to peritoneal surfaces and the consequent proliferation and invasion (Bulun, 2009; D'Hooghe, 2003).

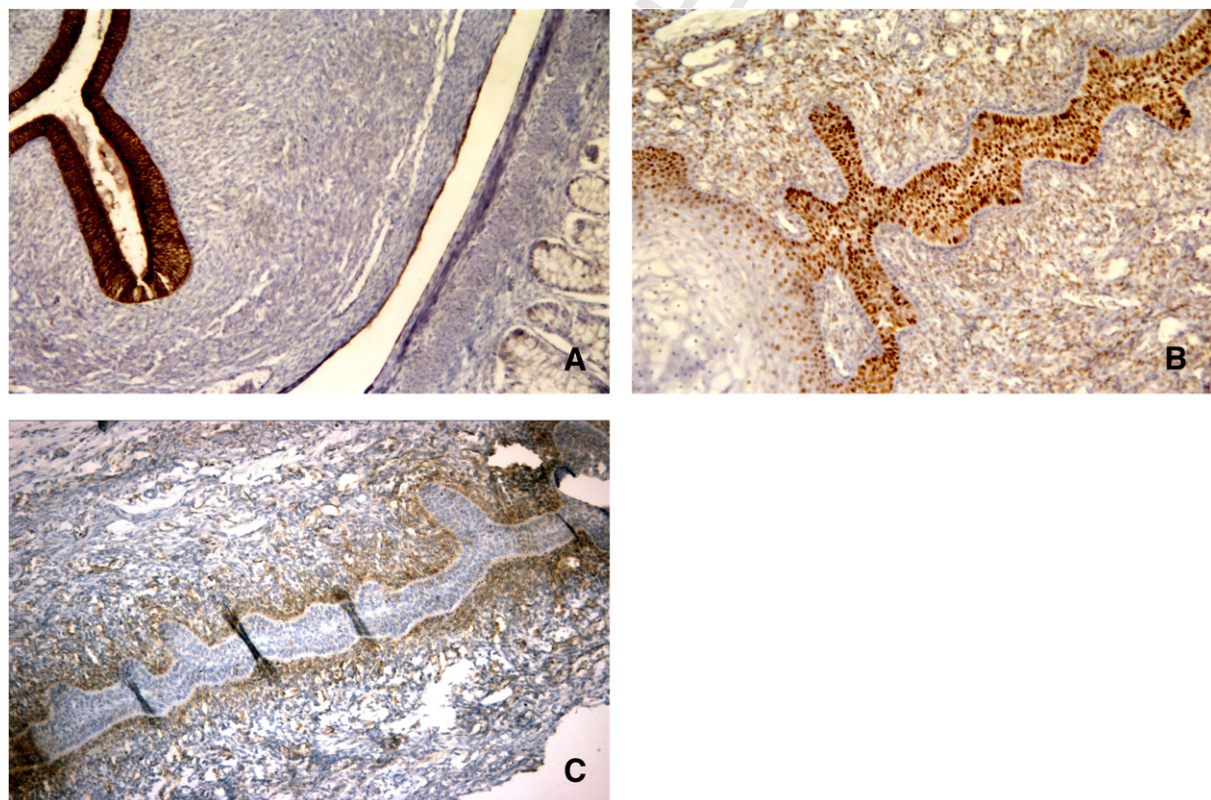


Figure 3 Immunohistochemical appearance of the eutopic endometrium in a female human fetus of 25 weeks of gestation. (A) Strong immunohistochemical expression of cytokeratin 7 in the eutopic endometrium. Note that the epithelium of the rectum visible in the right corner of the picture is completely negative for cytokeratin 7 expression (ABC, original magnification $\times 20$). (B) Strong immunohistochemical expression of oestrogen receptor in the eutopic endometrium (ABC, original magnification $\times 20$). (C) Strong immunohistochemical expression of CD10 in the stromal cells surrounding the primitive endometrium (ABC, original magnification $\times 20$).

Recently, the presence of ectopic endometrium has been demonstrated in a significant number of human female fetuses (four in 32 cases) analysed by autopsy (Signorile et al., 2009b). This observation has been the first direct and systematic demonstration of the theory of developmentally misplaced endometrial tissue as the cause of endometriosis. The new case presented here reinforces that observation and represents the first step towards a detailed and methodical analysis of this phenomenon. These data, indeed, beg the question as to why pathologists have never described this phenotype; this could be explained by the fact that these are very small lesions, located in a very specific anatomical area that is very rarely investigated during autopsy. In particular, this study carefully analysed the molecular phenotype of this ectopic endometrium, showing that it expresses characteristic markers of the epithelium and of the stroma of the genital tract, such as cytokeratin 7, CA125, oestrogen receptor and CD10. The histological and immunohistochemical analysis of the eutopic and ectopic endometrium shows a very similar phenotype. This observation argues against the possibility that this ectopic endometrium could disappear during the final steps of organogenesis. Interestingly, a similar CD10 staining pattern was also found in the cases of fetal endometriosis presented in Signorile et al. (2009b). It should also be noted that epithelial differentiation and distribution in the uterus occur in the human fetus in a similar way as in the adult (Barberini et al., 2007). Interestingly enough, the existence of choristoma composed of Müllerian remains in adults has been codified and named Mülleriosis, even if this phenomenon has been interpreted, but not demonstrated, as different from endometriosis (Batt et al., 2007). It is speculated that this ectopic endometrium would remain quiescent and asymptomatic until puberty, when the hormonal inputs would cause its regrowth and, consequently, the onset of the symptoms of endometriosis. The clinical and therapeutic implications of this observation are straightforward. Endometriosis should not be considered a recurrent disease and complete surgery can be curative; nevertheless, it would not justify post-operative hormonal treatments. Finally, taking into account the enormous problems of infertility caused by this disease, all information on the pathogenesis of endometriosis, could have important clinical implications for the management of associated infertility.

Nevertheless, these data do not confute the theory of reflux menstruation that is accepted by the majority of the workers involved in endometriosis research. It could be possible that, based on the secondary Müllerian system theory (Lauchlan, 1994), the same milieu of molecules operating *in utero* and indicated as responsible for the peritoneal implantation might facilitate extrauterine dislocation of endometrium during fetal development from the Müllerian ducts. Further studies in in-vitro and animal models are urgently required in order to fully investigate the Mülleriosis hypothesis and to determine its real clinical value.

1. Uncited references

Acien (1986) and Mai et al. (1998).

Acknowledgements

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