

EVIDENCE OF ADENOMYOSIS IN FETUSES: ANOTHER EMERGING PIECE IN RESOLVING THE ENDOMETRIOSIS PUZZLE

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BACKGROUND

Endometriosis affects approximately 10% of the female population in their reproductive years and represents one of the most common human diseases. The most widely accepted theory of origin is Sampson’s theory of reflux menstruation. Sampson’s classification of heterotopic endometrial tissue is based on pathogenesis :

- 1) “direct or primary endometriosis” [adenomyosis];
- 2) “peritoneal or implantation endometriosis”;
- 3) “transplantation endometriosis”;
- 4) “metastatic endometriosis”;
- 5) “developmentally misplaced endometrial tissue”.

METHODS

In order to test the hypothesis of congenital adenomyosis (“developmentally misplaced endometrial tissue”), we designed a prospective study of uteri in fetuses terminated spontaneously or for lethal malformations. Histology with systematic serial sections were performed in 420 fetal uteri.

FINDINGS

Adenomyosis was observed in a total of 10 (2,4%) fetuses aged from 19 to 37 weeks. There was no increase in the threshold toward adenomyosis in the fetuses presenting malformations of the uro-genital system.

INTERPRETATION

These data suggest that adenomyosis might be present from the fetal stage, with possible genetic backgrounds in some cases. Furthermore, our results enhance a novel etiopathogenetic concept of adenomyosis as a developmental defect of differentiation or migration of the mullerian duct system during embryogenesis.

Fig.1: Histological appearance of uterus in patient 5 (24 weeks).

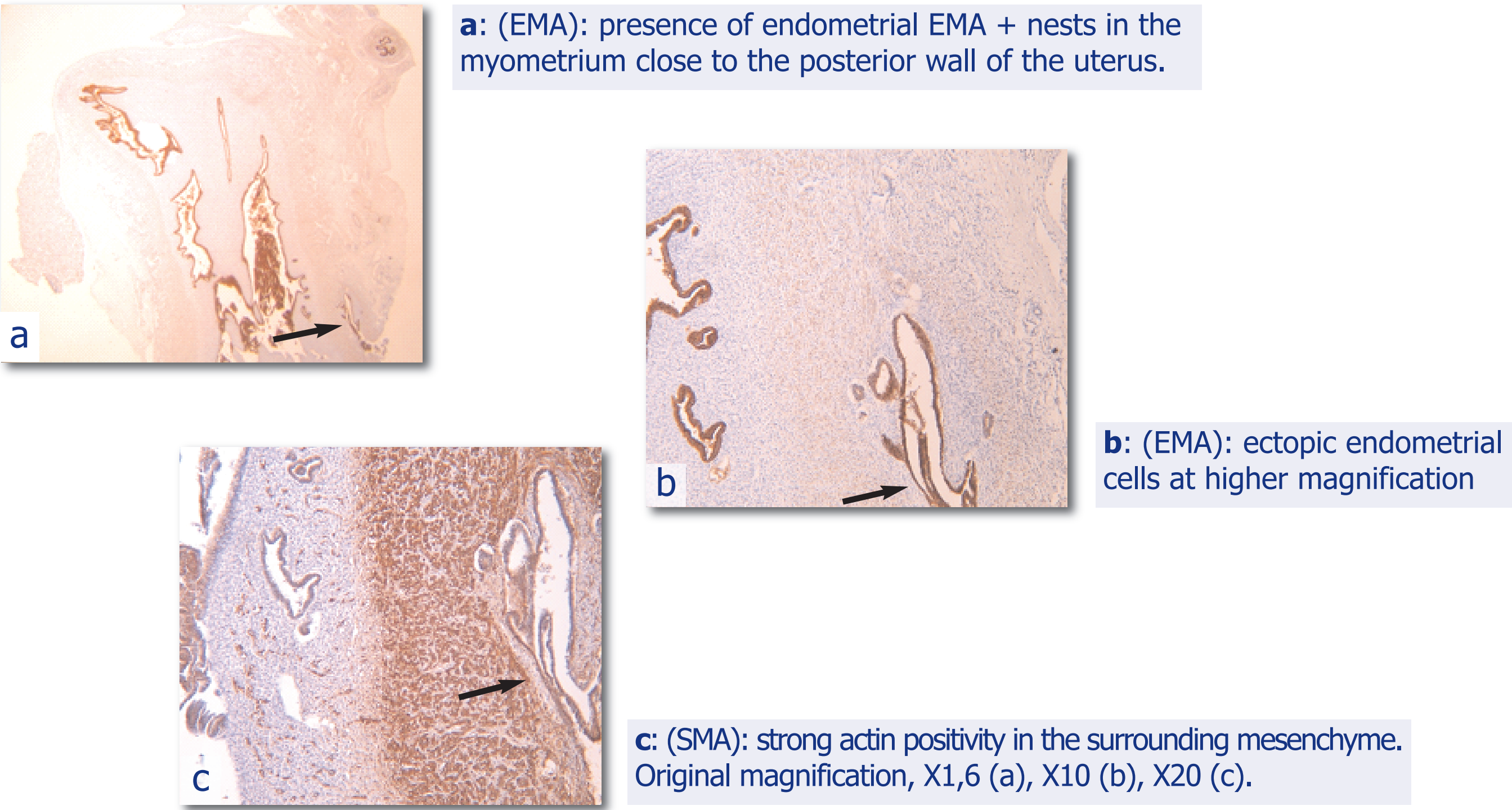


Fig.2: Histological and immunohistological appearance of uterus in patient 9 (26,5 weeks).

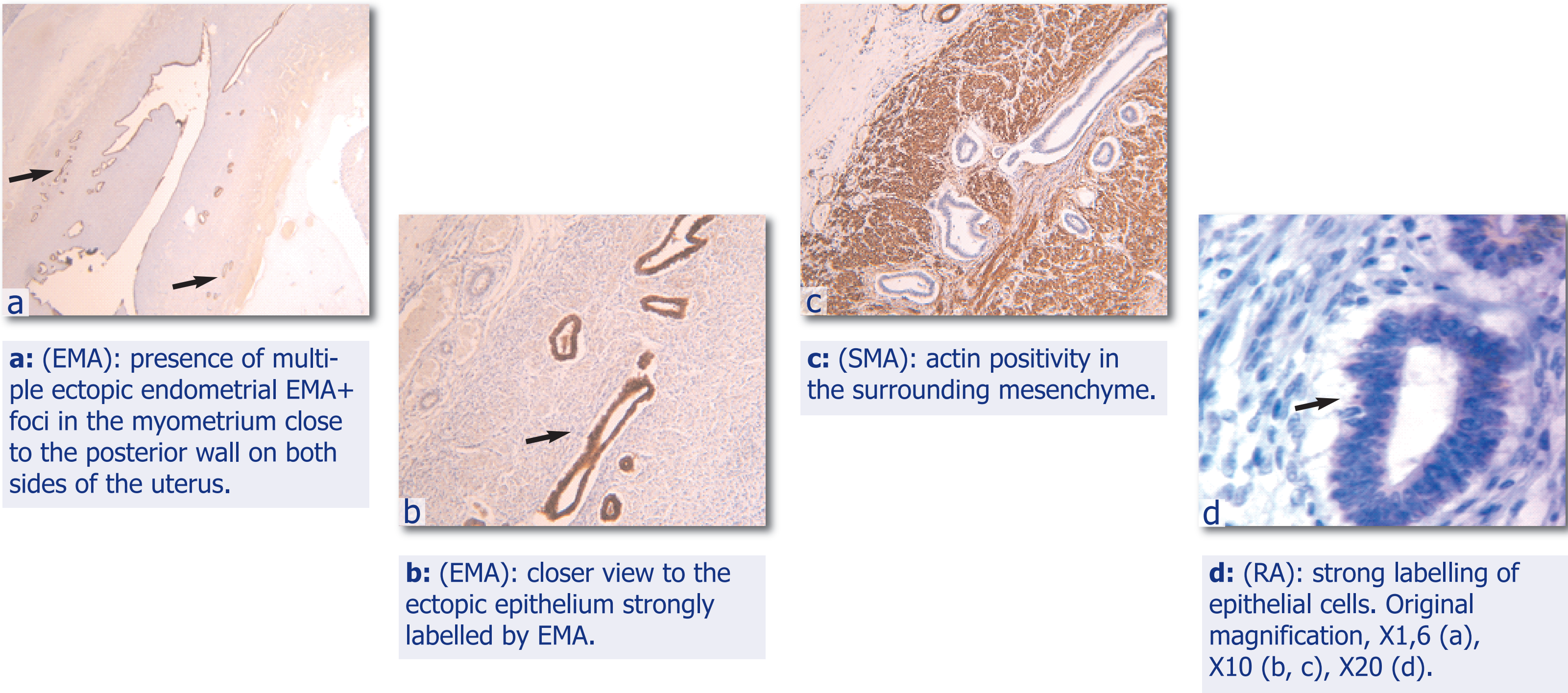
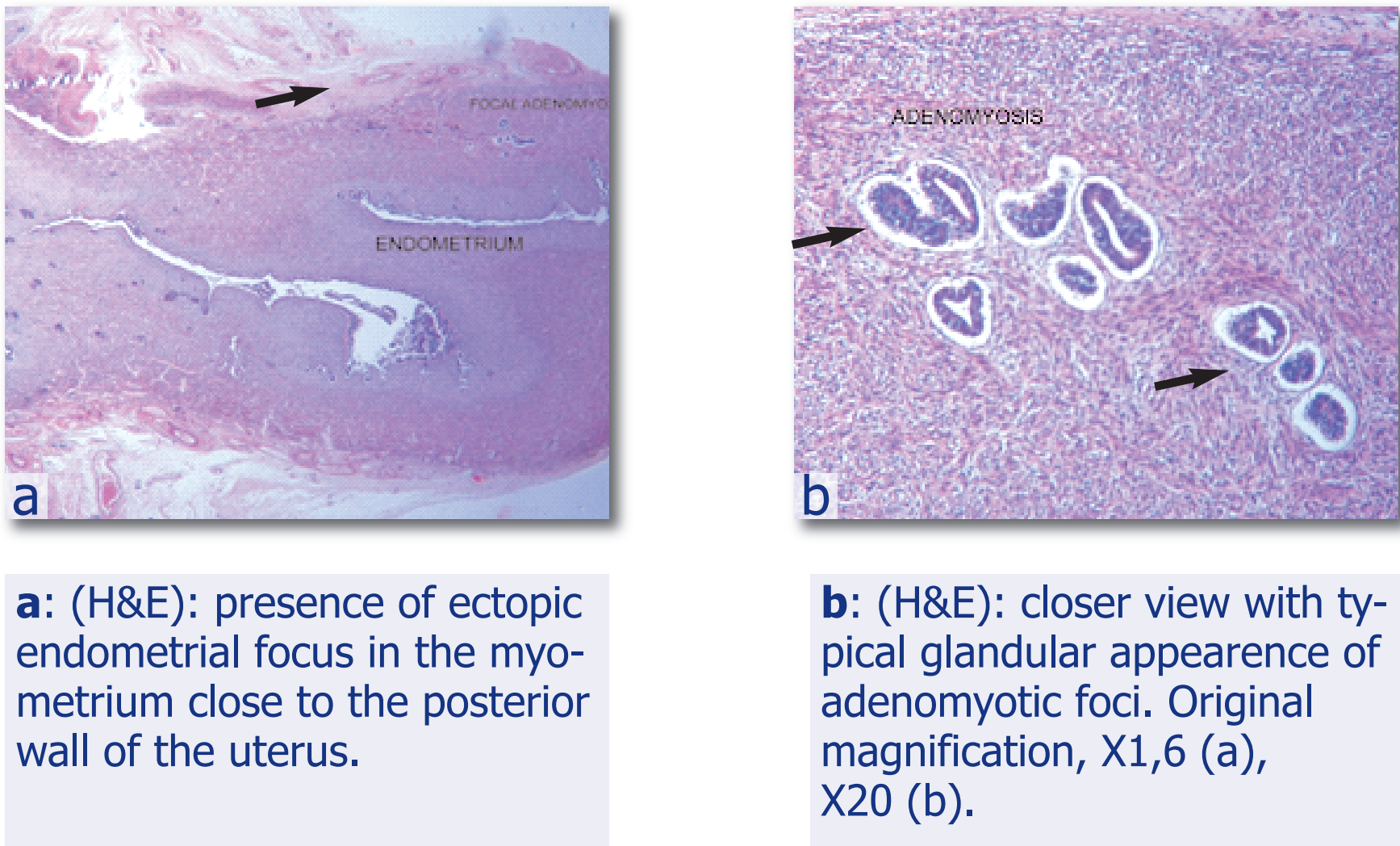


Table 1: Clinical features of the 10 patients presenting focal adenomyosis

PATIENT	GEST. AGE (wg)	IUFD/TOP	CARYOTYPE	CLINICAL FINDINGS	G/P
1	19	TOP	Trisomy 18	Growth retardation, Facial dysmorphia, Camptodactyly	G1
2	25	TOP	Normal	Bilateral renal agenesis	G1
3	18	TOP	Normal	Osteogenesis imperfecta	G2P0
4	37.4	Neonatal demise	Normal	Congenital Diaphragmatic Hernia	Non documented
5	24	TOP	Normal	Fetal Akinesia Deformation Sequence	G1
6	34	TOP	Normal	Cerebral anomalies	G5P0
7	27	IUFD	Normal	Pierre Robin, Adactyly / Syndactyly	G1
8	25.2	IUFD	Non performed	Placental vascular pathology	G4P3
9	26.5	TOP	Normal	Heart malformation, Clefting	G1
10	24	TOP	Normal	Cerebral anomalies	G1

Legend: **IUFD:** in utero fetal demise, **TOP:** termination of pregnancy, **wg** : weeks of gestation, **G/P** : gestity/parity

Fig.3: Histology of uterus in patient 2 (25 weeks).



REFERENCES

Adachi S, Tajima A, Quan J, Haino K, Yoshihara K, Masuzaki H, et al. Meta-analysis of genome-wide association scans for genetic susceptibility to endometriosis in Japanese population. J Hum genet 2010, Preprint sept16.

Attar R, Agachan B, Kuran SB, Toptas B, Eraltan IY, Attar E, Isbir T. Genetic variants of vascular endothelial growth factor and risk for the development of endometriosis. In Vivo 2010;24/3:297-301.

Budiu RA, Diaconu I, Christluis R, Dricu A, Edwards RP, Vlad AM. A conditional mouse model for human MUC1-positive endometriosis shows the presence of anti-MUC1 antibodies and Foxp3+ regulatory T cells. Dis Model Mech 2009;2:593-603.

D'Hooghe TM. Invisible Microscopic Endometriosis: How wrong is the Sampson hypothesis of retrograde menstruation to explain the pathogenesis of endometriosis? Gynecol Obstet Invest 2003;55:61-62.

Hansen KA, Eyster KM. Genetics and genomics of endometriosis. Clin Obstet Gynecol 2010;53/2:403-412.

Healy DL, Rogers PA, Hill L, Wingfield M. Angiogenesis : a new theory for endometriosis. Hum Reprod Update 1988;4/5:736-740.

King A, Burrows T, Loke YW. Human uterine natural killer cells. Nat Immun 1996;15:41-52.

Levgur M, Abadi MA, Tucker A. Adenomyosis: Symptoms, Histology, and Pregnancy Terminations. Obstet Gynecol 2000;95/5:688-691.

Robboy SJ, Bean SM. Pathogenesis of endometriosis. Reprod Biomed 2010;21/1:4-5.

Sasaki Y, Sakai M, Miyazaki S, Higuma S, Shiozaki A, Saito S. Decidual and peripheral blood CD4+CD25+ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. Mol Hum Reprod 2004;10:347-353.

Sasson IE, Taylor HS. Stem cells and pathogenesis of endometriosis. Ann NY Acad Sci 2008;1122:106-115.

Schumacher A, Brachwitz N, Sohr S, Engeland K, Langwisch S, Dolapchieva M, et al. Human chorionic gonadotropin attracts regulatory T cells into the fetal-maternal interface during early human pregnancy. J Immunol 2009;182:5488-5497.

Signorile PG, Baldi F, Bussani R, D'Armentio M, De Falco M, Boccellino M, Quagliuolo L, Baldi A. New evidence of the presence of endometriosis in the human fetus. Reprod Biomed 2010;21/1:142-147.

Tilburgs T, Roelen DL, van der Mast BJ, de Groot-Swings GM, Kleijburg C, Scherjon SA, Claas FH. Evidence for a selective migration of fetus-specific CD4+CD25bright regulatory T cells from the peripheral blood to the decidua in human pregnancy. J Immunol 2008;180:5737-5745.

Uno S, Zembutsu H, Hirasawa A, Takahashi A, Kubo M, Akahane T, et al. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. Nat genet 2010;42/8:707-710.

Zanatta A, Rocha AM, Carvalho FM, Pereira RM, Taylor HS, Motta EL, Baracat EC, Serafini PC. The role of the Hoxa10/HOXA10 gene in the etiology of endometriosis and its related infertility: a review. J Assist Reprod genet 2010;Preprint Sept 7.