Endometriosis in MRKH cases as a proof for the coelomic metaplasia hypothesis?

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Abstract

A diagnosis of endometriosis is based upon the histological identification of endometrial tissue at ectopic sites which are commonly located on the pelvic organs, the peritoneum and ovary. In rare cases, ectopic lesions can be found in other organs, such as kidney, bladder, lung or brain. Diagnosis is achieved by laparoscopic intervention followed by histological confirmation of endometriotic tissue. Prevalence is estimated at approximately 10% in the general female population with many patients experiencing pain and/or infertility. Currently, the implantation hypothesis by Sampson is the most accepted hypothesis about the pathogenesis of endometriosis. However, the occurrence of endometriosis in patients with Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome who sometimes lack a uterus or endometrium seems to suggest metaplasia as a cause of endometriosis. A critical reevaluation of the literature about MRKH does not reveal conclusive evidence of an association of uterus/endometrium agenesis and endometriosis. Most often only MRI diagnoses of uterus/endometrium agenesis and only very rarely conclusive histological evidence of the endometriotic lesions are presented. In contrast, whenever biopsies were performed endometriosis always appeared together with uterus/endometrium remnants. Taken together, we suggest that MRKH patients only develop endometriosis if a uterus/endometrium is present which underscores and not contradicts the implantation hypothesis of Sampson.

Introduction

In its simplest definition endometriosis is a disease characterized by the presence of endometrial glands and stroma outside of the normal localization (Clement 2007). Furthermore, irrespective of location, endometriotic glands almost always have an overtly endometrioid appearance and histologically resemble uterine endometrial glands (Clement 2007). Despite this straightforward histological definition, it is puzzling that endometriosis and endometriotic lesions show so many different facets, such as variations in color, depth of invasion, adhesions, ovarian cysts and different epithelial-to-stromal cell ratios up to the extreme case of stromal endometriosis (Guo 2018).

Retrograde menstruation followed by implantation of the endometrial tissue on different surfaces in the pelvic or abdominal cavity is generally accepted as the main cause of endometriosis (Sampson 1927). Despite the high rate of retrograde menstruation, only approximately 10% of women in their reproductive age acquire endometriosis (Bulun 2009) pointing to secondary factors affecting the adhesion and invasion of endometrial cells thus resulting in endometriosis. It has been hypothesized that peritoneal endometriosis, endometriomas and deep-infiltrating endometriosis (DIE) could represent three distinct entities, which do not share a common pathogenesis (Nisolle & Donnez 1997). Especially ovarian endometriosis (endometriomas) was postulated to be derived from metaplasia (Zheng et al. 2005).

Robert Meyer (1924) was the first to introduce the hypothesis that endometriosis may arise from coelomic epithelium. The female reproductive tract develops from a pair of Müllerian ducts, which arise from coelomic epithelial cells of mesodermal origin (Kurita 2011; Fig. 1). Then the Müllerian ducts undergo a transformation from single tubes consisting of homogeneous epithelium and surrounding mesenchyme into several distinct organs, namely the oviduct, uterus, cervix and vagina. The underlying mesenchyme hereby dictates the organ-specific cell fate of the coelomic epithelium. However, we should keep in mind, that the ovaries only contain remnants from the coelomic epithelium in form of the mesothelial surface. In mature reproductive tracts, the developmental plasticity of coelomic epithelial cells is mostly lost (Kurita 2011; Fig. 1).

In endometriosis, the process of metaplasia is postulated to involve the transdifferentiation of a committed cell type (e.g. mesothelium) into an alternative cell type (e.g. endometrial epithelium). Recently,
etiology of MRKH is still unresolved (Rall et al. 2013, Ledig & Wieacker 2018). Although treatment options for MRKH are scarce (Londra et al. 2015), recently, treatment with a tissue-engineered vagina has gained some attention (Raya-Rivera et al. 2014).

**Uterus and endometrium in MRKH patients**

Several studies with large cohorts of MRKH cases showed that 48–99.2% MRKH patients still have a rudimentary uterus (Oppelt et al. 2012, Hall-Graggs et al. 2013, Marsh et al. 2013, Rall et al. 2013, Preibsch et al. 2014, Lalatta et al. 2015, Pan & Luo 2016, Wang et al. 2017). In three studies (Oppelt et al. 2012, Lalatta et al. 2015, Pan & Luo 2016) the numbers of aplastic uteri are not clearly specified. Most often magnetic resonance imaging (MRI) and ultrasound have been used to evaluate the presence of the uterus (Table 1). It is generally agreed that MRI is the modality of choice for further evaluation of all uterine anomalies (Londra et al. 2015). In a case series of MRKH patients (n=214) an overall correlation above 95% between MRI and laparoscopic findings was reported for 115 patients (Preibsch et al. 2014), which included 75% of patients with bilateral uterine rudiments, 15% with unilateral uterine rudiments and only 10% with complete uterine agenesis. In 85% of cases where uterine rudiments were removed, the presence of endometrial tissue was adequately diagnosed by MRI (Preibsch et al. 2014); however, 15% of endometria were missed by MRI.

Histological analysis from biopsies of MRKH patients demonstrated an endometrium in 40.5% (17/42; Rall et al. 2013), in 48% (23/48; Marsh et al. 2013) and in 100% (9/9; Wang et al. 2017) of the cases.

**MRKH and endometriosis**

In PubMed we searched for articles describing an association between MRKH and endometriosis. We identified 21 manuscripts, 19 of which were case reports (Table 1). Most of the authors identified MRKH by MRI and/or ultrasound and presented some evidence of endometriosis, especially of ovarian endometriosis and adenomyosis. Interestingly, in 7 out of 18 articles describing uterus remnants also endometria could be identified (Table 1). It remains unclear whether in the ten articles with uterine remnants, endometria were missed, because these assumptions were mostly based upon MRI or ultrasound. As shown in a comparative study, MRI detection of uterine remnants agreed in 77.3% with laparoscopy (Preibsch et al. 2014), thus demonstrating that MRI is not sufficient to prove the absence of uterus remnants. Additionally, the sensitivity of ultrasound in the detection of uterine remnants is even lower (Lermann et al. 2011).

Remarkably, in only 11 articles a biopsy of the uterus was undertaken and only three manuscripts presented histologic evidence of uterus/endometrium (Table 1). Furthermore, in only five articles histology of the endometriotic lesions was presented (Table 1). Enatsu et al. (2000) showed an endometrial/adenomyotic gland, but without an identifiable myometrium and the whole uterus not shown, the evaluation of adenomyosis is not conclusive (Fig. 2A, B and C). Furthermore
Table 1  Findings of MRKH and endometriosis ordered chronologically.

<table>
<thead>
<tr>
<th>Authors</th>
<th>CR or OR</th>
<th>Patients (N)</th>
<th>MRKH</th>
<th>Endometriosis</th>
<th>Uterus endometrium</th>
<th>Biopsy uterus</th>
<th>MRI</th>
<th>US</th>
<th>CT</th>
<th>Histology uterus</th>
<th>Histology lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enatsu et al. (2000)</td>
<td>CR</td>
<td>1</td>
<td>Yes</td>
<td>Agenesis</td>
<td>Uterine remnant</td>
<td>Done</td>
<td>n.d.</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>Partly shown</td>
</tr>
<tr>
<td>Doyle &amp; Laufer (2009)</td>
<td>CR</td>
<td>2</td>
<td>Yes</td>
<td>One case with endometriosis, unspecified</td>
<td>Both with uterus remnants</td>
<td>Done</td>
<td>n.d.</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>Shown</td>
</tr>
<tr>
<td>Yan et al. (2011)</td>
<td>CR</td>
<td>1</td>
<td>Yes</td>
<td>Endometrioma</td>
<td>Uterine remnant</td>
<td>n.d.</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>Shown</td>
</tr>
<tr>
<td>Elliott et al. (2011)</td>
<td>CR</td>
<td>1</td>
<td>Yes</td>
<td>Endometrioma</td>
<td>Endometrium, uterine remnant</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Chun et al. (2013)</td>
<td>CR</td>
<td>1</td>
<td>Yes</td>
<td>Adenomyosis</td>
<td>Endometrium, uterine remnant</td>
<td>Done</td>
<td>n.d.</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>Shown</td>
</tr>
<tr>
<td>Marsh et al. (2013)</td>
<td>OR</td>
<td>48</td>
<td>Yes</td>
<td>5 unspecified cases</td>
<td>Endometrium, uterine remnant</td>
<td>Done</td>
<td>n.d.</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Kawano et al. (2014)</td>
<td>CR</td>
<td>1</td>
<td>Yes</td>
<td>Endometrioma</td>
<td>Endometrium, myometrium</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>n.d.</td>
<td>Shown</td>
</tr>
<tr>
<td>Troncon et al. (2014)</td>
<td>CR</td>
<td>1</td>
<td>Yes</td>
<td>Endometrioma</td>
<td>Uterine remnant</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Hoo et al. (2016)</td>
<td>CR</td>
<td>1</td>
<td>Yes</td>
<td>Adenomyosis</td>
<td>Uterine remnant</td>
<td>n.s.</td>
<td>n.d.</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Wang et al. (2017)</td>
<td>OR</td>
<td>92</td>
<td>Yes</td>
<td>Adenomyosis</td>
<td>Uterine remnant</td>
<td>n.d.</td>
<td>Done</td>
<td>Done</td>
<td>Done</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

CR, case report; CT, computed tomography scan; MRI, magnetic resonance imaging; n.d., not done; n.s., not shown; OR, original research; US, ultrasound.
the diagnosis of adenomyosis in MRKH patients is debatable because endometrial islands have been described as typical for MRKH patients (Ledig & Wieacker 2018).

In the figures presented by Yan et al. (2011; Fig. 2D) and Cho et al. (2009; Fig. 2E), no ovarian lesions are visible. Only Chun et al. (2013) showed a cyst of ovarian endometriosis (E) of an MRKH patient; however, no cyst is visible. In contrast, Chun et al. (2013) presented a normal endometrium (F) and an adenomyosis (G) of an MRKH patient.

**Discussion**

**Metaplasia of ovarian epithelial and stromal cells?**

Because in MRKH patients most often endometriomas were found, we will focus on the possibility of ovarian metaplasia. In a study about endometriomas, Zheng et al. (2005) categorized them as type 1 (or initial) when the endometriotic tissue was localized on the ovarian surface, which can result in endometrial glands in the ovarian stroma (OStr). (B) After invagination of the OSE and formation of an inclusion cyst (IC), metaplasia to an endometriotic gland (EG) occurs. E, ectopic endometrial epithelium; EG, endometriotic gland; OSE, ovarian surface epithelium; OStr, ovarian stroma; Str, endometrial stroma.

they performed immunohistochemical analysis and found aromatase-positive epithelial/stromal cells and CD10-positive stromal cells in endometriomas type 1. They concluded that metaplasia did arise from transition of ovarian surface epithelial cells to endometrial epithelial cells and could be observed in endometriomas type 1 (Zheng et al. 2005). Although Zheng et al. (2005) mentioned metaplasia of the ovarian stromal components, no hypothesis was suggested whether the endometriotic stromal cells are generated from OSE or ovarian cortex cells. Recently, however, we could show that nearly all epithelial cells in all endometriomas were positive for keratin 18 and keratin 19 (Konrad et al. 2018a) a protein pattern that has never been found for ovarian surface epithelial cells. Thus, the transition of ovarian surface epithelial cells into endometrial epithelial cells seems highly unlikely as no intermediate cell types between OSE and endometriotic cells could be identified. Similarly, a transition of ovarian cortical or OSE cells to endometriotic stromal cells could not be observed (Konrad et al. 2018b).

Of note, Matsuura et al. (1999) used a coculture system of OSE and ovarian stromal cells in a 3D collagen lattice treated with 17β estradiol in which the OSE formed a lumen structure, surrounded by endometrial stromal cells with an epithelial mesenchymal structure. Immunohistochemistry with epithelial membrane antigen and cytokeratin was positive for the glandular cells, which also demonstrated tight junctions. Thus, Matsuura et al. (1999) suggested that endometriosis may manifest as a serial change from the adjacent mesothelial cells. Unfortunately the purity of the OSE by for example calretinin was not evaluated to exclude the possibility of contaminating tubal/endometrial epithelial cells. Furthermore the ‘newly’ formed endometrial stromal cells were not stained with CD10 to confirm endometriosis of at least the stromal cells.

Discussion of possible metaplasia models

Although very rarely mentioned, metaplasia of ovarian cells into endometriotic cells requires the differentiation into two distinct cell phenotypes, epithelium and stroma (Fig. 3). However, it still remains unclear whether this process starts from one cell type (e.g. mesothelium) or rather two cell types which then undergo metaplasia into two distinct cell types (stromal and epithelial). If we think about metaplasia of the mesothelium to generate ovarian endometriosis, rectovaginal cells to generate DIE or myometrial muscle cells (or other endometrial cell types) to generate adenomyosis, we have to postulate that in order to become endometrial stromal and endometrial epithelial cells very different cell types in very different surroundings must undergo the same ‘endometrial metaplasia’ program(s) whose initiating factor(s) are still unknown. Although such a scenario is highly unlikely, it was recently shown that approximately 17% of cortical ovarian inclusion cysts were paired boxed gene 8 (PAX8)- and calretinin double-positive. This points to metaplasia of calretinin-positive PAX8-negative inclusion cysts into PAX8/calretinin double-positive inclusion cysts (Park et al. 2018). Normally, OSE cells are calretinin -positive and PAX8 negative, whereas the secretary cells of the tubal fimbria are negative for calretinin and positive for PAX8. Although Park et al. (2018) did not analyze the surrounding stroma of the cortical inclusion cysts in detail, no obvious histological characteristics other than ovarian cortical stroma could be seen.

Although metaplasia as a cause of endometriosis is very often mentioned (Nisolle & Donnez 1997), only very rarely calretinin was used as a marker for peritoneal mesothelial cells or OSE to show metaplasia. To the best of our knowledge, we could identify only four manuscripts where endometriosis was immunohistochemically analyzed with calretinin, but none of them described a positive calretinin staining of endometriomas (McCluggage et al. 2003), liver cysts (Hsu et al. 2014), occult microscopic endometriosis in the peritoneum (Khan et al. 2014) or in a post-cesarean section scar (D’Agostino et al. 2019).

Conclusions

The best non-invasive choice for the diagnosis of MRKH is MRI, however, in up to 15% of cases uterus remnants are missed (Preibsch et al. 2014). Thus, in our opinion it is not sufficient to demonstrate uterus agenesis in MRKH patients (Balci et al. 2008, Cho et al. 2009) to be associated with endometriosis without confirmation by biopsy. Exceptional claims need exceptional evidences. We suggest that it is mandatory to present the histology of the uterus/endometrium remnants (if possible) and also from the endometriotic lesions to prove unequivocally uterus agenesis together with endometriosis; otherwise any conclusion of metaplasia is not substantiated. In cases of uncertainty the use of tissue biomarkers such as CD10 for stromal endometrial/endometriotic tissue (McCluggage et al. 2001) or other biomarkers such as calretinin for mesothelial cells (McCluggage et al. 2003) is indicated and conclusive histological pictures together with immunohistochemical evidence should be presented. As clearly shown in this manuscript the claim that the occurrence of endometriosis in MRKH patients is an indication of metaplasia and thus a counterargument to the implantation hypothesis by Sampson is not based on unequivocal proofs. Whenever uterine biopsies were performed endometriosis always appeared together with uterus/endometrium remnants in MRKH cases. Thus MRKH patients only develop endometriosis if a uterus/ endometrium is present which underscores and not contradicts the implantation hypothesis by Sampson.
Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Endometriosis and the MRKH syndrome

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Received 5 July 2018
First decision 7 September 2018
Revised manuscript received 11 March 2019
Accepted 11 April 2019