

Review

Coexistence of mature cystic teratomas and endometriosis

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Mature cystic ovarian teratomas are ovarian tumors that are most common in reproductive age women. MCTs are benign germ cell tumors that arise from totipotent germ cells in the ovary. Endometriosis is also a common gynecologic disease affecting reproductive age women. Endometriosis is a progressive and chronic disease associated with inflammation, chronic pelvic pain, and infertility. However, the pathophysiology, symptoms, diagnosis, and management of each disease are well known, but there is little information on the simultaneous occurrence of these two diseases. Therefore, the epidemiology, clinical symptoms, imaging, management, and the risk of malignant transformation of the coexistence of MCTs and endometriosis are discussed herein. PubMed and any reports of individuals with both MCTs and endometriosis were searched for all articles written in the English-language medical literature until May 2020. This review indicates that diagnosis and treatment of the coexistence of MCTs and endometriosis are more complicated when two diseases coexist than when only one disease exists. In conclusion, this comorbid conditions may not be as rare as it was previously thought. To understand and treat this complex condition, more studies are essential.

Keywords

Mature cystic ovarian teratomas; endometriosis; coexistence

1. Introduction

Mature cystic teratomas (MCTs), also known as dermoid cysts, are the most common benign ovarian tumors in women of reproductive age. MCTs are germ cell tumors that originate from totipotent germ cells which develop into fully differentiated endodermal, mesodermal, and ectodermal tissue [1]. Most of MCTs have few symptoms even if they are quite larger. They are often found incidentally on routine physical examination or imaging or when surgery is performed for other causes. Therefore, surgery is often performed in an emergency in cases with symptoms such as acute abdominal pain due to torsion.

Endometriosis is a common and debilitating gynecologic disorder which affects mostly reproductive age women. It is an estrogen-dependent disease characterized by the presence of endometrial glands and stroma outside the uterine cavity, often associated with inflammation, chronic pain, and infertility [2]. To relieve symptoms

such as pain or to improve fertility, surgery is performed.

Although MCTs and endometriosis are benign ovarian tumors encountered frequently in women of childbearing age, the coexistence of these two diseases has been reported in only a few case reports so far. However, a few studies describing the coexistence of MCTs and endometriosis directly or indirectly have been published recently [3, 4, 5, 6]. Therefore, the author intended to gather and organize available knowledge to help find the clinical implications of this rare and challenging condition and establish a framework for diagnosis and treatment.

2. Search strategy for coexisting mature cystic teratomas and endometriosis

PubMed and any reports of individuals harboring both MCTs and endometriosis were searched for all articles written in the English-language medical literature to May 2020 using the keywords 'coexistence', 'endometriosis', and 'teratoma'. All reports were carefully assessed and their references were also reviewed.

3. Epidemiology and clinical findings

MCTs are the most common type of germ cell tumors accounting for 15% of all ovarian tumors and 43%-70% of benign ovarian tumors [7]. They comprise approximately 70% of benign ovarian tumors in women under 30 years of age and 50% of pediatric tumors [8]. However, most MCTs are asymptomatic, so the reported prevalence may have been reported to be lower than they actually are. Studies on the location of MCTs are controversial. Some studies reported conflicting results [9], but the results that MCTs occur more on the right side are dominant [10, 11, 12]. In addition, they can be located at the midline and in paraxial regions of the body and unusual locations, including lungs or ilea [13]. In approximately 10-15% of cases, they are on both sides [14].

Most of MCTs are asymptomatic. They are discovered incidentally by routine physical examination, radiologic examinations, or during surgery performed for other pathologies [6]. However, they can cause acute complications including ovarian torsion, infection, rupture, or malignant transformation [15].

Endometriosis is a common gynecologic condition characterized by the presence of endometrial glands and stroma outside the uterine cavity, which affects approximately 7-10% of women in the reproductive age [16]. However, among infertile women, endometriosis increases up to 20-50% and in women with pelvic pain to 30-80% [17]. Endometrioma is the cystic tumor within the ovary

with ectopic endometrium tissue lining and is found to be in 17%-44% of women with endometriosis [18]. Ovarian endometriosis has been reported to affect 20% of women with endometriosis [19]. Endometriosis occurs more frequently on the left side than the right side [20, 21, 22]. The hypothesis of this claim has been explained because of the barrier role of the sigmoid colon [20]. Bilateral ovarian endometriosis has been reported to affect 19-28% of cases [23]. Endometriosis has been reported to involve commonly uterus, fallopian tubes, intestine, and uterosacral ligaments. It has been reported to involve rarely the vagina, urinary bladder, ureter, lungs, gastrointestinal tract, bones, and central nervous system [17].

Symptoms of endometriosis range from asymptomatic to extreme pain, enough to interfere with daily life. The main symptom is pelvic pain, but other symptoms include dysmenorrhea, deep dyspareunia, and dyschezia [24]. In addition, 20% of women with endometriosis suffer from subfertility [25].

So far, four studies have mentioned the prevalence of the coexistence of MCTs and endometriosis. Matalliotaki et al. evaluated the association between benign gynecological tumors and endometriosis in 1,000 women with endometriosis [3]. They showed that MCTs were found in 1.5% of women with endometriosis. Thereafter, Matalliotakis et al. evaluated the association between ovarian dermoid cyst (teratoma) and endometrioma [4]. They showed that the coexistence of ovarian teratoma with endometriosis detected in 4.6% (8/172) of women and with endometrioma in 2.9% (5/172). They found the simultaneous coexistence of 13 cases with endometriosis or endometrioma. They also found 6 patients with dermoid cyst and endometriosis or endometrioma in the same ovary. In a study of 80 patients with MCTs, Kurt et al., tried to find out their association with fertility and to detect the rate of malignant degeneration [5]. They found that MCT was encountered in 9 patients during examination for infertility, 6 of whom had accompanying endometriosis. According to their research, the coexistence of MCTs and endometriosis was detected in 7.5% (6/80) of women. Recently, Heesuk Chae evaluated the incidence of endometriosis in women with mature cystic ovarian teratoma and analyzed the clinicopathologic features of this occurrence [6]. According to the study, a total of 71 patients were included, of which 55 (77.46%) had teratoma and 16 (22.54%) harbored the coexistence of endometriosis and MCTs.

Based on the case reports and a study about the coexistence of MCTs and endometriosis, clinical findings of this rare condition were reviewed. Thirteen case reports describing the coexistence of MCTs and endometriosis were found, for a total of 14 individuals with pathological features of both MCTs and endometriosis (Table 1). The size of the cyst is represented by the largest diameter. The location of the cyst was only marked with lesions of the coexistence of MCTs and endometriosis. For bilaterally, the size is noted in parentheses at each location. In case 2, teratomas were found in both ovaries and endometriosis was a peritoneal type. In case 13, teratoma was in the right ovary and endometriosis was in the left ovary. The mean age of 14 patients of the case reports was 29.4 years (range 22-35 years). The average age of patients with this rare condition was 27.38 ± 5.60 years [6]. Judging from the two results, the coexistence of MCTs and endometriosis reveals that it occurs in young women. In addition, regarding symptoms, case 7 may be suffering from ectopic pregnancy, so the calculations excluded case 7.

The most common symptom of the 13 patients in these case reports was dysmenorrhea (6/13, 46.2%). This result was the same as that of the Chae's study [6]. This latter study showed that the majority of patients with teratoma alone were asymptomatic (24/55, 43.6%) and the lesions were discovered incidentally during routine ultrasound examination, whereas the most common symptom in patients with the coexistence of mature cystic teratoma and endometriosis was dysmenorrhea (7/16, 43.8%) [6]. Therefore, the author mentioned that a gynecologic symptom such as dysmenorrhea in patients with this rare condition may be an important diagnostic clue.

Table 1 shows that 53.8% (7/11) of the cases were on the left side, whereas 36.4% (4/11) were on the right. Case 2 was excluded because of peritoneal endometriotic lesions whereas case 9 was excluded because there was no detailed mention about the location of the cyst. Case 13 was also excluded because endometriosis occurred on the left and teratoma on the right. There is a hypothesis as to why the majority of endometriomas are located in the left ovary. The hypothesis is that the origin of endometriosis is regurgitated endometrial cells and furthermore the presence of the sigmoid colon may be related to decrease fluid movement in the left side of the pelvis [22]. In those teratomas observed frequently in the right side, Vercellini et al. suggested a different pathogenesis of the two entities [38].

To summarize the above, the coexistence of MCTs and endometriosis occurs frequently in women of reproductive age. The most common presenting symptom in patients with this rare condition may be dysmenorrhea and the location has not yet been confirmed.

4. Imaging

Ultrasonography has been the 1st choice method for diagnosing MCTs. One study showed that the sensitivity and specificity for transvaginal ultrasonography in the diagnosis of cystic teratoma were 57.9% and 99.7%, respectively [39]. Representative ultrasound findings are as follows: The first is a cystic lesion with a densely echogenic tubercle called Rokitansky nodule projecting into the cyst lumen [40]. The second is an echogenic mass with sound attenuation by hair and sebaceous material within the cyst cavity [41]. The last ones are multiple echogenic and thin bands caused by hair within the cyst cavity [42]. Other radiologic modalities are computed tomography (CT) and magnetic resonance imaging (MRI). CT findings of teratomas include large amounts of fat attenuation within ovarian cyst, with or without calcification in the wall of the cyst [43]. On MRI, the sebaceous component of dermoid cyst parallels the signal intensity of fat on all sequences [42, 44]. It is easy to make a diagnosis if the teratomas have the typical image findings mentioned above. However, ovarian teratomas can be associated with various complications, including torsion (16% of ovarian teratomas), rupture (1%-4%), malignant transformation (1%-2%), infection (1%), and autoimmune hemolytic anemia (< 1%) [42, 45, 46]. In cases of complicated teratomas, unusual imaging manifestations may lead to misdiagnosis.

The most commonly used imaging modalities to diagnose endometriosis are transvaginal ultrasonography and MRI. Transvaginal ultrasonography also has been the first-line imaging examination. Mais et al., showed that using a characteristic ultrasonographic finding (round-shaped homogenous hypoechoic "tissue" of

Table 1. Summary of the reported cases describing coexistent endometriosis and mature cystic ovarian teratoma.

No	Reference	Age (yrs)	Number of cases (n)	Presenting symptom	Side	Size of cyst (cm)	Intraoperative findings	Treatment
1	Caruso et al, 1997 [26]	28	1	Abdominal pain	Lt	5		cystectomy
2	Frederick et al, 2003 [27]	27	1	Dysmenorrhea		Rt (6), Lt (4)	Severe adhesion	cystectomy
3	van der Merwe et al, 2010 [28]	30	1	Abdominal distension	Rt	40	Severe adhesion	oophorectomy
4	Sindilar et al, 2011 [29]	30	1	Abdominal pain	Lt	6		cystectomy
5	Chen et al, 2011 [30]	35	1	Abdominal pain	Rt	7	Severe adhesion	cystectomy
6	Prorocic et al, 2012 [31]	33	1	Dysmenorrhea	Lt	5.5	Adhesion	cystectomy
7	Chae et al, 2015 [32]	28	1		Lt			cystectomy
8	Taylor et al, 2015 [33]	33	1	Incidentally	Rt	9	Adhesion	oophorectomy
9	Wagner et al, 2015 [34]	34	1	Dysmenorrhea	Both			cystectomy
10	Hwang et al, 2017 [35]	22	1	Flank pain	Lt	3		cystectomy
11	Darouichi et al, 2017 [13]	33	1	Pelvic pain	Lt	8		cystectomy
12	Kiyak et al, 2018 [36]	25	Case 1	Pelvic pain, dysmenorrhea	Lt	13	Severe adhesion	cystectomy
		22	Case 2	Dysmenorrhea	Rt	6		cystectomy
13	Rokhgireh et al, 2019 [37]	31	1	Dysmenorrhea	Rt: teratoma Lt: endometrioma	Rt (9) Lt	Adhesion	cystectomy

low-level echoes within the ovary), transvaginal ultrasonography has an efficiency of 88% in differentiating endometriomas from other ovarian masses with a specificity of 90% [47]. MRI for endometriosis is usually performed when the ultrasonographic findings are inconclusive or if malignancy is suspected. Hottat et al. studied the accuracy of MRI imaging in the preoperative assessment of endometriosis and then showed that sensitivity and specificity were 96.3%, 100%, respectively [48]. CT is not effective in diagnosing endometriosis because it cannot see the pelvic organs well, but it is useful in cases such as ureteral involvement [49].

There is little information regarding the diagnosis of the coexistence of MCTs and endometriosis. Therefore, considering only the patients mentioned in Table 1, nearly all patients, excluding cases 7, 11 and 12, were not diagnosed before surgery. MRI was performed in 4 cases, 1 case was suspected of malignancy, and the rest diagnosed this rare condition (data not shown). Several methods have been suggested as a way to distinguish teratoma from endometriosis, and they are as follows: chemical-shift artifact in the frequency-encoding direction [50], phase-shift gradient-echo imaging [51], and sequences with frequency-selective fat saturation technique [42]. This rare disease such as the coexistence of MCTs and endometriosis presents challenges not only to clinicians but also to radiologists. In the end, getting used to the imaging features of this rare condition will help the differential diagnosis.

5. Management

Because benign ovarian cysts such as MCTs occur most commonly in the reproductive age women, it has been accepted as the standard strategy that cystectomy is performed to preserve healthy ovarian tissue as much as possible. In women at perimenopause or postmenopause, adnexectomy or oophorectomy is the method of choice. Laparoscopy has become the gold standard technique in the management of benign ovarian tumors. Compared with laparotomy, laparoscopic surgery has many advantages such as shorter re-

covery time, cosmetic benefits, and less postoperative pain [8, 52]. According to studies comparing laparoscopy and laparotomy, laparoscopy has a greater risk of cyst rupture and spillage of the cyst content than laparotomy [53, 54]. Thus, laparotomy will be feasible if the cyst is large or exists bilaterally or if malignancy is suspected.

Laparoscopy has become the gold standard for the management of endometriosis. The European Society of Human Reproduction and Embryology guidelines recommend that surgical approach should be performed in women complaining of pain associated with endometriosis or in women with endometrioma greater than 3 cm [55]. Surgery should be performed to remove visible lesions and restore the normal anatomic structure. However, in the cases of advanced endometriosis, the possibility of conversion to laparotomy or oophorectomy due to severe adhesions should be discussed before operation.

For MCTs, spillage of the contents due to intraoperative rupture of teratoma has been reported to be associated with chemical peritonitis and adhesion formation [8, 56]. Post-operative adhesions due to spillage of the contents may result in problems such as infertility [56]. The risk of intra-operative spillage is reported to be in 40-50% of cases during laparoscopic cystectomy, compared to 10-15% during laparotomy with cystectomy [57, 58, 59]. Caspi et al. suggested that because the mean growth rate of MCTs in premenopausal women is 1.8 mm/year, premenopausal women with MCTs of < 6 cm in diameter can be safely managed expectantly, especially if pregnancy is desired [60]. O'Neil et al. mentioned that given asymptomatic status, the small size of the lesions, torsion, rupture, and low risk of malignancy, expectant management is reasonable. In addition, many studies reported that ovarian function after cystectomy for ovarian endometrioma may be impaired [61, 62]. Exacoustos et al. reported that endometrioma, unlike MCTs, was associated with a significant decrease in residual ovarian volume which may result in diminished ovarian reserve and function [63]. Furthermore, the possibility that ovarian function was already im-

paired due to the presence of endometrioma was raised [64, 65, 66]. Given the above results, discussion on whether to perform surgical treatment or conservative treatment for benign ovarian cysts is ongoing.

The coexistence of MCTs and endometriosis can further complicate the problem of treatment. In Table 1, 7 out of 14 (50%) cases showed adhesions during surgery, 4 of which exhibited severe adhesions. Chae H. [6] showed that in patients with coexistence of MCTs and endometriosis when compared with patients harboring MCTs alone, the size of the cyst was larger and the operation time was longer. In addition, advanced-stage endometriosis (stage III or IV) was present in 8 out of 16 (50%) patients with this rare concurrence. In order to prevent spillage of the contents of MCTs, a method of removing cysts in an endobag has been proposed [67]. However, it is difficult to apply this method in cases with large cyst or with adhesion. Finally, the probability of spillage of the cyst content during laparoscopic cystectomy is much higher than in the cases of only MCTs. In addition, the researcher found that damage to ovarian reserve after surgery was also greater in patients with MCTs alone [6]. Kurt et al. reported that MCTs can be present concurrent with endometriomas, but infertility is prominent in patients with concurrent endometriosis [5]. According to Shi et al. endometriotic cells of endometriomas synthesize and secrete transforming growth factor beta 1 (TGF- β 1), which promotes surrounding ovarian tissue fibrosis and adhesion, eventually rendering the cystectomy surgery difficult and loss of ovarian tissue inadvertently [68]. Taken together, unlike MCTs alone, this rare condition of coexistence of MCTs and endometriosis has the characteristic of endometriosis. Compared to MCTs, in those cysts of this rare condition, cysts are not well separated from healthy ovarian tissue, and hence ovarian function after surgery may be reduced.

6. Recurrence and malignant transformation

MCTs are known as benign tumors with a high recurrence rate. Anteby et al., reported that women with bilateral or multiple dermoid cysts are more likely to recur later [69]. Lagerbe et al. showed that ovarian cystectomy performed by laparoscopy when compared to laparotomy, is associated with a significantly higher risk of recurrence [70]. Harada et al. reported a long-term recurrence rate of 4.2% after surgical excision of MCTs. In this respect, patients with young age (< 30 years old), large cyst (\geq 8 cm in diameter) or bilateral cysts, are at high risk of recurrence. For endometriosis, recurrence after surgery is the problem. The reported recurrence rate was high, estimated as 21.5% at 2 years and 40-50% at 5 years [71].

Twenty-seven percent of patients are readmitted to the hospital for additional surgery, 12% of which undergo hysterectomy [72]. Because there is no data on the recurrence of coexistence of MCTs and endometriosis, this point cannot be addressed at the moment, however it can be inferred that the probability of recurrence after surgery is very high in this rare concurrence because both endometriosis and MCTs recur easily.

Malignant transformation of MCTs was found in 1%-2% of MCTs [73]. More than 80% of malignant transformation are squamous cell carcinoma, the rest are carcinoid tumors or adenocarcinomas [74]. Malignancy occurs in older women with mean age of 45-60 [75]. Kikkawa et al., showed that a tumor larger than 9 cm

in dimension was 86% more prone for malignant transformation in their series [76]. Santos et al. showed that the average diameter was 14.2 cm, indicating that larger tumors correlate with an increased risk of malignant transformation [73]. Many studies have attempted to reveal the relationship between endometriosis and ovarian cancer. Ovarian cancer in women with endometriosis is found to be with an occurrence rate of 0.3-1.6% [77, 78, 79]. Brinton et al. showed that the risk of ovarian cancer was particularly increased in patients with a long-standing history of ovarian endometriosis [80]. A cohort study showed that ovarian cancer associated with endometriosis occurs in two histologic subtypes: endometrioid and clear cell [81]. Gadducci et al. reported that the malignant transformation of ovarian endometriosis occurs in 0.7-2.5% of patients [82].

MCTs, the most common form of malignant transformation of MCTs (squamous cell carcinoma), endometriosis, and two histologic subtypes of malignant transformation of endometriosis (clear cell and endometrioid) are reviewed in the literature in order to find cases with malignant transformation of the coexistence of MCTs and endometriosis. Primary squamous cell carcinoma arising from endometriosis of ovary cases were excluded, and cases of malignant transformation from teratoma (endometrioid carcinoma or clear cell carcinoma) were also excluded. A total of three cases were found, and a case report was written in English [83]. The rest of cases were reported in Japanese and hence excluded [84, 85]. Shimura et al. [83] reported a 71-year-old patient who underwent surgery with a tumor up to 40 cm in the right ovary. The pathologic diagnosis was MCT, endometriotic cyst, clear cell carcinoma, clear cell adenofibroma, and clear cell borderline tumor. However, even in this case, the author suggested that clear cell adenofibroma, not endometriosis, had developed into clear cell carcinoma, so it cannot be regarded as malignant transformation of the coexistence of MCTs and endometriosis.

7. Conclusions

MCTs and endometriosis are the most common benign diseases in reproductive age women, but little research has been conducted on the simultaneous occurrence of these two diseases. Therefore, unlike MCTs or endometriosis alone, diagnosis and treatment of endometriosis can be a challenge for clinicians and radiologists. However, judging from the above evidence, if women diagnosed with MCTs complain of dysmenorrhea, it is important to be aware of the possibility of coexisting endometriosis. Also, if the cyst size is large or the menstrual cramps are getting worse, it may be more appropriate to make an accurate diagnosis and treatment plan through a surgical approach rather than conservative management. However, further research on the coexistence of MCTs and endometriosis is warranted because knowing the incidence of the disease, risk factors and an understanding of the pathophysiology of this rare condition, will serve as a guide in establishing a proper treatment protocol.

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Conflict of interest

The author declares no conflicts of interest.

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