Dear Editor and Reviewers,

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled " Giant exophytic cystic adenomyosis with an ectopic Mirena after uterine myomectomy: A case report and literature review"(ID: 51175). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significant to our case report. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the manuscript. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

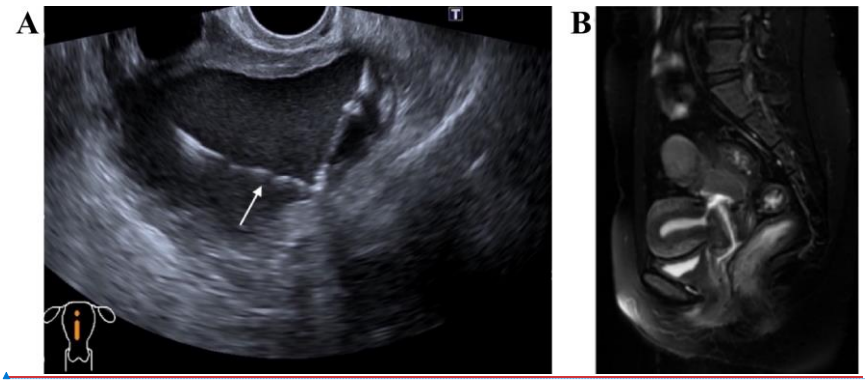
Responds to the Reviewer's comments:

Reviewer #1: I read with great interest the manuscript "Giant exophytic cystic adenomyosis with an ectopic Mirena after uterine myomectomy: A case report and literature review" I have following few comments. Please provide some insights to the laboratory examination performed e.g. Hb, CA-125 etc These tests are also important to check for any superadded infection, pyosalpinx etc.

Response: The routine blood test (June 28, 2017) showed a WBC count of 7.3 × 10^9/L, neutrophils percentage of 63%, RBC count of 3.6 ×10^{12}/L, haemoglobin concentration of 138 g/L, and platelet count of 192 × 10^9/L. The carbohydrate antigen 125 level was 8.0 IU/L, and the C-reactive protein level was 1.3 μg/ml.

1. Please elaborate the ultrasound findings in terms of echogenicity, uterine contour, volume, myomectomy remnants if present.

   Response:



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(A)

The B-mode ultrasound showed an anterior and normal uterus size and a cystic echogenic mass that measured 9.5*7.4*7.4 cm located at the posterior uterine isthmus. The white arrow indicates an IUD contained within this cystic mass. There was no myomectomy remnants observed in the ultrasound examination.

2. What was the presumptive diagnosis based on the MRI. Was there a clinical diagnosis?

Response: Based on the MRI, the presumptive diagnosis and of a LNG-IUD contained within the pelvic endometrial cyst was proposed.

Based on the imaging data and her history, the patient was clinically diagnosed with a endometriosis cystic mass located at the posterior uterine isthmus after myomectomy, a LNG-IUD out of the uterine cavity.

3. How was the bleeding pattern, intensity of dysmenorrhea and Hb level noted , was it been recorded for no of days, months, years? and at what time you could see change in the resolution.

Response: The patient's menstrual volume and pattern in the previous 7 days were the same as those before the operation, and then mild bleeding continued for approximately 5 days. Since the LNG-IUD insertion, she became amenorrhea. Because the patient had no dizziness, fatigue and anemia appearance, hemoglobin concentration changes were not monitored. However, haemoglobin concentration （138g/L） was normal when the patient was admitted to the hospital.

The patient started dysmenorrhea only 2 years before admission. The pain was recurrent in nature, associated with menstruation and exacerbated monthly, enough to incapacitate her routine activities. Thereafter, she experienced progressively worsening dysmenorrhea, refractory to any medication. Since the IUD insertion, dysmenorrhea completely disappeared.

The patient has been relieved from her symptoms of dysmenorrhea and abnormal uterine bleeding, starting from the first menstrual period after surgery to date. The menstruation was clean within 7 days.

4. More history is needed for the IUD insertion and what type of method was used to reconstruct the uterine wall. This is crucial for good obstetrical outcome.

Response: We feel really sorry for our carelessness， the history of the IUD insertion is as follow:
At a consultation in another hospital six months earlier, the B-mode ultrasound findings showed a cystic mass of approximately 9 cm in diameter located at the posterior uterine isthmus, and a LNG-IUD was inserted into the “uterine cavity”. Since the IUD insertion, her dysmenorrhea completely disappeared, and amenorrhea commenced. Three months before the referral, the IUD was outside of the uterine cavity and a giant cystic echogenic mass was detected by B-mode ultrasound in our outpatient department.

The method used to reconstruct the uterine wall is as follow:
Continuously suturing the entire uterine wall twice.

6.Figures, Ref- OK With due respect to author's efforts and expertise. Thanks
Response: Thanks for your encouragement.

Reviewer #2: The manuscript describes an original case report dealing with a giant cystic adenomyosis. The authors believe that the giant cystic adenomyosis could derive from the opening of uterine cavity during a previous laparoscopic myomectomy. The authors also report an improvement of the symptoms of the patient

after insertion of a levonorgestrel containing intrauterine device into the giant cystic adenomyosis However, the manuscript has some limitations and issues that remain to be solved.

Major points:

1. The authors should improve Key Words. Ectopic, Surgery, exophytic, Case report do not reflect the focus of the manuscript. “Levonorgestrel containing intrauterine device” should be used instead of Mirena.

Response: Thanks for your help. The keyword “ case report” was written in accordance with journal format requirements.

The Key Words is modified as follow: Cystic adenomyosis; dysmenorrhea; levonorgestrel containing intrauterine device; myomectomy; case report

We have used “Levonorgestrel containing intrauterine device” instead of Mirena throughout the manuscript.

2. The authors should explain why looking at TIMELINE (line 54) laparoscopic myomectomy was performed on June 2011, but looking at History of past illness (line 69, 70) laparoscopic myomectomy was performed on 2013.

Response: We feel really sorry for our carelessness.

The laparoscopic myomectomy was performed on 2011.

3. Looking at the intravenous pyelography one cannot say that the intrauterine device is “ectopic”. Therefore, Figure 1A is useless and should be removed from the revised manuscript.

Response: We have made correction according to the comment. Figure 1A was removed.

4. The Discussion is mainly focused on the role played by Mirena (better “Levonorgestrel containing intrauterine device”) on the symptoms of the patient. This part of the discussion should be shortened in the revised manuscript.

Response: We have made correction according to the comment.

Interestingly, in this case, the LNG-IUD was actually inserted in the adenomyosis cyst instead of the uterine cavity, but the symptoms of abnormal uterine bleeding and

dysmenorrhea were markedly relieved, which raises a question about the role that the LNG-IUD played. The direct effect of levonorgestrel on the foci of the adenomyosis can affect the progesterone receptor, which produces a profound effect on the eutopic endometrium that becomes atrophic and inactive[10]. The consequences are hypomenorrhea and even amenorrhoea. In this unique case, levonorgestrel probably acted directly on the endometriotic lesions and on the normal endometrium via haematogenous or lymphatic pathways to reduce bleeding [11,12]. In addition, LNG-IUDs may also emerge as a good method for the reduction of pelvic vascular congestion[13], inhibition of the mediators of inflammation and reduction of macrophage activity present in the peritoneum to control pain associated with endometriosis [14].

5.By contrast, the hypothesis that the giant cystic adenomyoma could derive from the opening of uterine cavity during the laparoscopic myomectomy performed in 2011 (or 2013?) is not well discussed. The authors should support their hypothesis with relevant publications in the revised manuscript.

Response: We have made correction according to the comment.

There exist a number of hypotheses regarding the pathogenesis of adenomyosis, and one hypothesis recognized by most people is the endometrial injury invagination theory[4]. The peristalsis and contraction of the uterus originate from the endometrial myometrial interface called the junctional zone. When trauma such as caesarean delivery, myomectomy or curettage occurs at the junctional zone[5], a mechanism of tissue injury and repair will be activated, which results in increased local levels of E2[6]. Local hyperestrogenism is thought to lead to enhanced proliferation of endometrial cells and increased peristalsis of the junctional zone; hyperperistalsis allows ‘‘invasion’’ of the endometrium into the myometrium from the opening of the junctional zone, and the proliferated endometrium stimulates local uterine smooth muscle hypertrophy[7]. Moreover, excessive peristalsis will further damage the junctional zone, and then, the tissue injury and repair mechanism are re-activated again. This process forms a vicious circle that eventually leads to the development of adenomyosis[8]. When there are extensive endometrial secretory changes and haemorrhages in the endometrium that invades the myometrium, a cystic adenomyosis will develop[2].

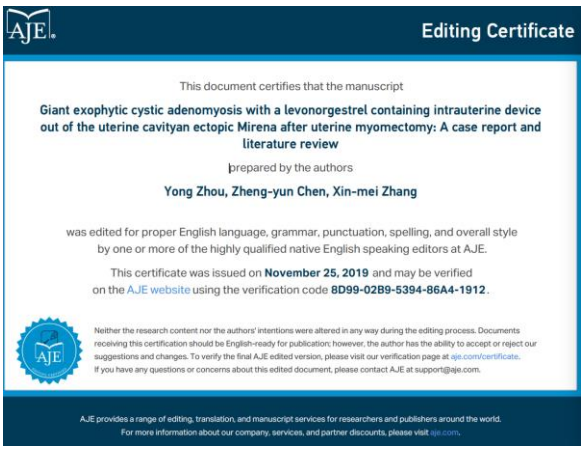
As the classification is based on cyst location in the uterine wall, cystic adenomyosis is subdivided into 5 subtypes [9]: Subtype A1 includes the submucous or intramural cystic adenomyosis; Subtype A2 includes cases of cystic polypoid lesions; Subtype B1 includes subserous cystic adenomyosis; Subtype B2 includes cases with exophytic growth; and Subtype C comprises uterine-like masses within the uterus.

Here, we reported a huge cystic adenomyosis that was suspected to be closely related to a prior uterine myomectomy history, which is supported by the following evidence. First, our patient began to experience abnormal uterine bleeding right after she underwent myomectomy as a result of the accumulated blood slowly outflowing from the cyst through the fistula that communicated with the cervical canal. Second, the cystic lesion was located at the site of the previous surgical wound, and the endometrial layer was broken through during myomectomy, inevitably causing damage to the junctional zone. Third, the patient suffered from progressively refractory dysmenorrhea in the past two years as the cyst gradually increased in size, which could be attributed to the collected intra-cystic secretions and periodic monthly bleeding that accumulated in the cyst. For these reasons, we believed that a prior uterine myomectomy could be the main predisposing factor for the transitional endometrium violating the myometrium, which involved in the pathogenesis and development of cystic adenomyosis.

Minor points:

1. In spite of the enclosed “Non-Native Speakers of English Editing Certificate.pdf” dated 2017, the manuscript still needs English language editing.

Response: We have completed the English language editing.



Editing Certificate

This document certifies that the manuscript

Giant exophytic cystic adenomyosis with a levonorgestrel containing intrauterine device out of the uterine cavityan ectopic Mirena after uterine myomectomy: A case report and literature review

prepared by the authors

Yong Zhou, Zheng-yun Chen, Xin-mei Zhang

was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at AJE.

This certificate was issued on **November 25, 2019** and may be verified on the AJE website using the verification code **8D99-02B9-5394-86A4-1912**.

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2. I suggest to use “Levonorgestrel containing intrauterine device” instead of Mirena throughout the manuscript.

Response: Thanks for your help. We have made correction according to the comment.

3. Why the authors use “ectopic” for the IUD found into the giant cystic adenomyoma? I think that “out of the uterine cavity” should be better used.

Response: Thank you very much.

We have made correction according to the comment.