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Review

Endometrial adenocarcinoma arising in adenomyosis: case report and review of literature

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Summary

Adenomyosis is a common benign gynecological condition in women of reproductive age. While endometrial cancer co-existing with adenomyosis is common, endometrial carcinoma arising from endometrial cells within adenomyosis (EC-AIA) is rare. We present an unusual case of EC-AIA in a 62-year-old woman with no clinical symptoms. EC-AIA should be considered as a different diagnosis from concurrent endometrial cancer and adenomyosis. EC-AIA should also be considered in adenomyosis patients with intact endometrium and vaginal bleeding and in those with a history of adenomyosis at reproductive age regardless of the occurrence of vaginal bleeding. Periodic follow-up is recommended in women diagnosed with adenomyosis at reproductive age.

Key words: Adenomyosis; Endometrial cancer; Endometrial adenocarcinoma.

Introduction

Adenomyosis is characterized by the presence of endometrial glands in the myometrium and is a common benign gynecologic condition in reproductive-aged women. The typical symptoms of adenomyosis are; progressive dysmenorrhea, abnormal uterine bleeding, and an enlarged uterus, which seriously affect the quality of life in these women [1]. The disease is classified into diffuse or focal adenomyosis, according to the extent and location. Of these, focal adenomyosis is termed adenomyoma. There is no precise mechanism for the migration and implantation of endometrial cells outside the endometrium. The tissue injury and repair (TIAR) model was suggested by Leyendecker [2]. The TIAR theory implied that, microtrauma of the endometrial-myometrial interface induces inflammation and estrogen production which causes uterine peristalsis and angiogenesis. These factors result in endometrial invagination and formation of adenomyotic lesions [2]. The characteristics of invagination and angiogenesis are similar to that of endometrial cancer. The relationship between adenomyosis and endometrial cancer have been of interest for many years. While endometrial cancer co-existing with adenomyosis is common [3], endometrial carcinoma arising from endometrial cells within adenomyosis (EC-AIA) is rare. Here, we report the case of an asymptomatic endometrial carcinoma localized in an adenomyoma.

Case Report

A 62-year-old postmenopausal woman with no gynecological symptom and an unremarkable medical history was referred to our outpatient department with an abdominopelvic computed tomography (APCT) image. The APCT image showed a hypodense lesion of about 55 mm in the uterus suggestive of a tumor (Figure 1). The serum levels of cancer antigen 125 and carcinoembryonic antigen were 12.4 U/mL (0-35 U/mL) and 1.8 ng/mL ($<$ 2.5 ng/mL), respectively. A transvaginal ultrasound revealed a uterine mass (55 $\times$ 54 $\times$ 49 mm) at the fundus with blood supply (Figure 2). We suspected a uterine sarcoma. The patient underwent total abdominal hysterectomy with both salpingo-oophorectomy and appendectomy. During the surgery, a white thumb-sized lesion was observed on the uterine surface. However, both adnexa were seen to be normal and there was no evidence of metastasis to the peritoneum and omentum. Specimens from the uterus and both adnexa were sent to the pathology department for analysis. We requested a frozen section analysis based on the white lesion mentioned above; an adenomyosis with hyperplastic lesions were observed. The surgery was then completed.

Pathological examination revealed the size of the uterus and mass to be 9.5 $\times$ 7.5 $\times$ 4.0 cm and 6.0 $\times$ 4.5 $\times$ 4.0 cm, respectively (Figure 3). The cut surface of the uterus was white-to-yellow. The histopathology of the uterine mass revealed an intramural adenomyoma containing a well-differentiated endometrioid carcinoma (grade 1). The lesion showed negative staining for p_{53}. Moreover, the nuclei showed mild to moderate atypia with inconspicuous nucleoli. The mitotic index was very low. An endometrial intraepithelial carcinoma (EIC) was also seen within the adenomyoma. The lesion was localized in the adenomyoma. The histopathologic findings are shown in Figure 2. The carcinoma was restricted to the adenomyoma and the resection margin was less than 1 mm from the uterine serosa. Due to the multifocal nature of the carcinoma throughout the adenomyoma lesion, the exact size of the carcinoma could not be measured. There was no lymphatic or vascular invasion. The margin of the adenomyoma on the opposite

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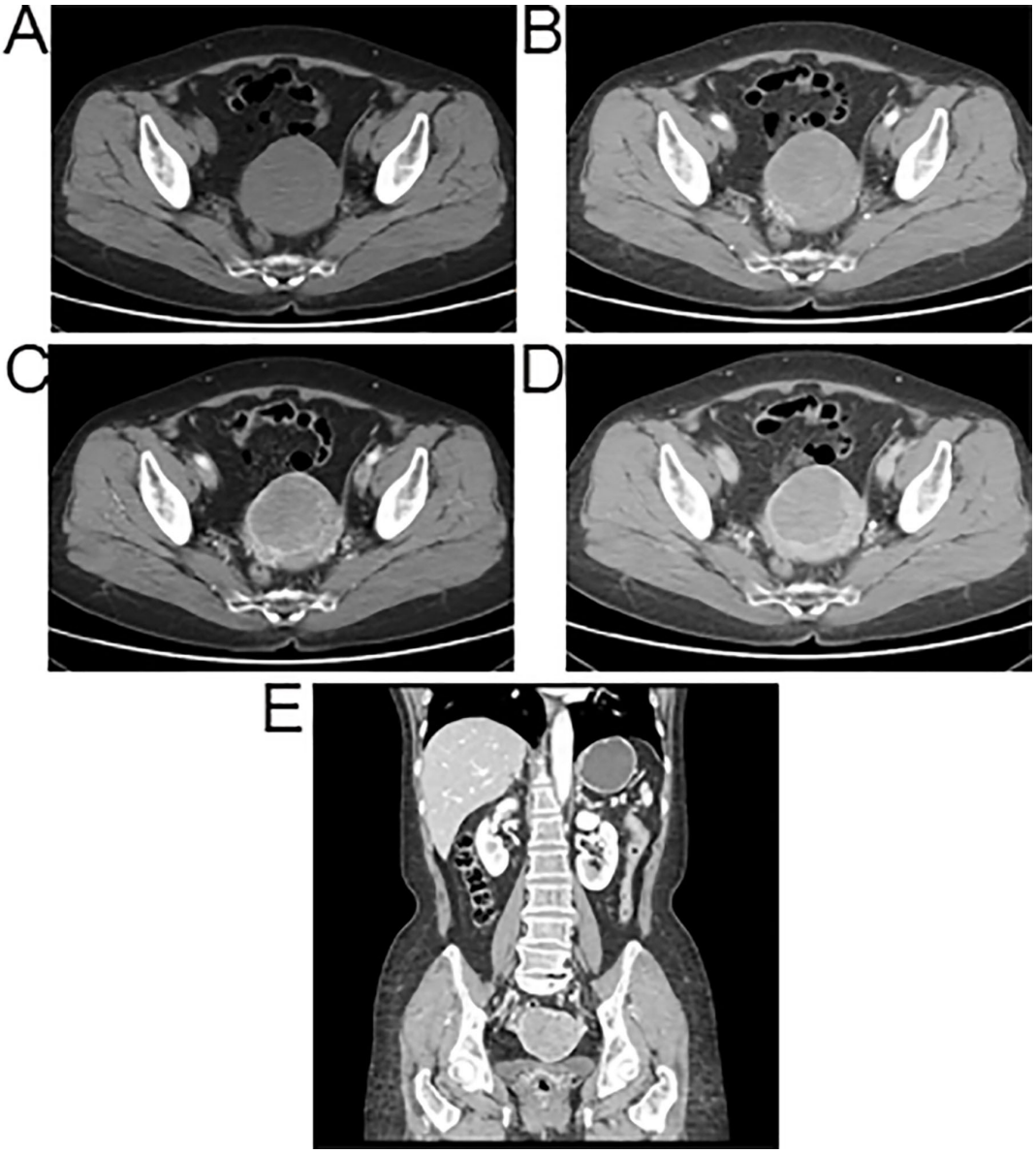

Figure 1. — Abdominopelvic computed tomography (CT) findings. The CT shows a pelvic mass with a hypodense lesion (approximately 5.5 cm) in the uterus. (A) Pre-contrast image. (B) Arterial phase image. (C) Portal phase image. (D) Delayed phase image. (E) Sagittal plane image.

side of the serosa was carcinoma-free. The endometrium was unremarkable. The cervix was not involved and both ovaries were atrophied.

She was diagnosed with a stage IB tumor (T1bNXM0). Positron emission tomography-computed tomography (PET-CT) was performed to plan an appropriate adjuvant treatment strategy. PET-CT revealed a hypermetabolic lymph node in her external iliac area, which seemed more like a reactive hyperplasia than metastasis. Based on this, we decided to administer no adjuvant treatment. A follow-up abdominopelvic CT performed 6 months later revealed no recurrence.

Discussion

Endometrial cancer arises from the endometrium and occurs mostly in postmenopausal women. Zhang *et al.* reported that 9.47% of patients with endometrial cancer also had adenomyosis [4]. Koji Matsuo *et al.* found that endometrial cancer patients with adenomyosis had a better survival outcome (both disease-free survival and overall survival) [5] possibly due to the mechanical blockage of endometrial carcinoma invasion into the myometrium. However, EC-AIA is very rare and not much is known about the disease progression and prognosis. The criteria for EC-AIA as described by Colman and Rosenthal are as follows: i) the carcinoma must not be located in the endometrium or elsewhere in the pelvis, ii) the carcinoma must be seen to arise

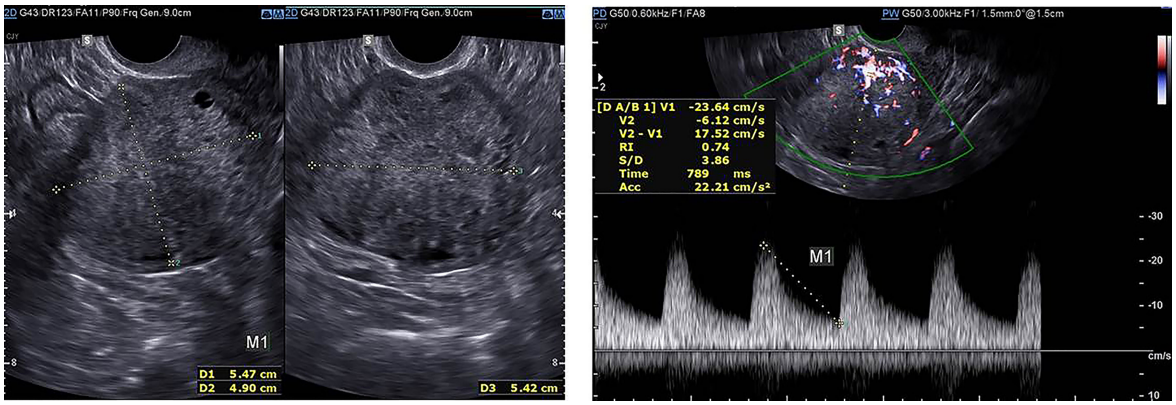

Figure 2. — Transvaginal ultrasound findings. Transvaginal ultrasound shows a uterine mass of size 55 × 54 × 49 mm on the fundusss with blood supply (RI 0.74).

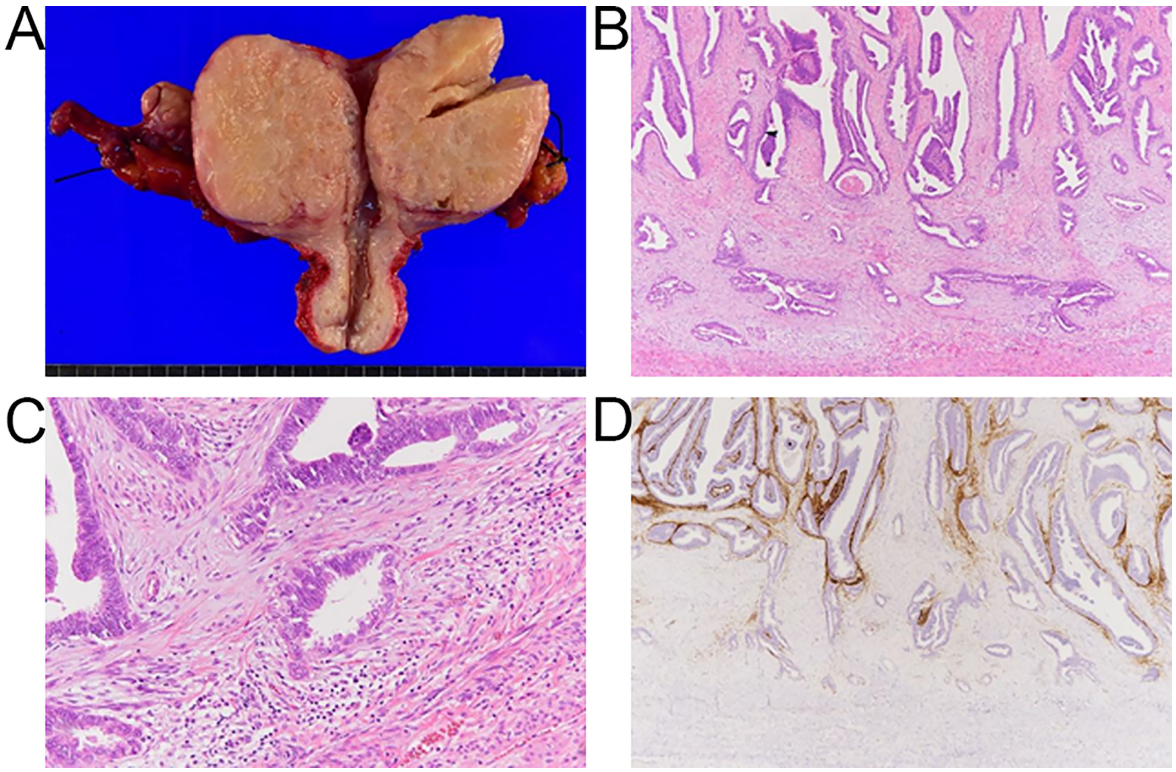

Figure 3. — Histopathologic findings. (A). Macroscopic findings of the uterus. (B). Myometrium showing a tumor composed of endometrial glands and endometrial-type stroma surrounded by smooth muscle (hematoxylin-eosin [H&E], original magnification × 40). (C). The peripheral portion of the tumor shows an endometrioid adenocarcinoma displaying an acinar and papillary architecture lined by stratified columnar epithelium with a crowded, complex, and branching architecture. The cytoplasm of the neoplastic cells is eosinophilic and granular. The nuclear atypia is mild to moderate, with inconspicuous nucleoli (H&E, × 200). (D). The brown-colored area shows an endometrial-type stroma. The peripheral portion of the tumor (lower side) shows the absence of an endometrial-type stroma, indicating a cancerous change (CD 10, × 40).

from the epithelium of the adenomyosis and not to have invaded from another source, and iii) endometrial (adenomyotic) stromal cells must be present to support the diagnosis of adenomyosis [6]. Our case met the above criteria. In our case, the endometrial cancer arose from the endometrial tissue inside the adenomyosis and the endometrium was free from cancer. Some previous reports have described EC-AIA cases including a few without endometrial involvement, as in our case. We used the term “adenomyosis and serous cancer” (from 2000 to 2020) to search PubMed for relevant English-language articles

Table 1. — *Cases of EC-AIA published from 2000 to 2020.*

Reference	n[a]	Age	C.C[b]	Stage	Histology of endometrium	Carcinoma subtype	Treatment	Adjuvant therapy	Follow-up
[11]	3	62	AUB[c]	IC	Atrophic	Endometrioid	TAH c BSO c PLND c PALND[d]	CTx[e] × 6	1 y survival
		72	Abdominal pain (RLQ[f])	IC	Atrophic	Clear Cell	TAH c BSO[g]	RT[h]	5 y died
		69	AUB	IA	Atrophic	Serous carcinoma	TAH c BSO c PLND c PALND		8 y survival
[9]	1	47	AUB	IA	Proliferative without atypical or hyperplastic lesion	endometrioid	TAH c BSO c PLND c PALND		1 y survival
[10]	1	61	AUB	Not mentioned	Atrophic	Serous carcinoma	TAH c BSO	RT	3 y survival
[8]	1	54	Pelvic pain	Not mentioned	Unremarkable	Endometrioid	TAH c BSO	CTx	1 y survival
[15]	1	57	AUB	IB	Normal	Endometrioid (G1)	Semiradical hysterectomy c BSO c PLND c	CTx × 5 (TC[i])	5 y survival (recur at 5 y)
[14]	1	67	No Symptom	IB	Unremarkable	Endometrioid(G2)	TAH c BSO	CTx × 6(TC)	16-month survival
[7]	1	40	frequency and abdominal mass	IB	Normal	Clear cell	TAH[j]		6-month survival
[13]	1	64	LLQ pain	IIIA	Atrophic	Serous carcinoma	TAH c BSO	CTx × 1 (TC)	1-month survival
[12]	1	67	Right inguinal mass and AUB	Not mentioned	Unremarkable	Not mentioned	Complete staging surgery with inguinal lymph node dissection	CT × (TP[k])	8-month survival

[a] Number of cases; [b] Chief complaint; [c] Abnormal uterine bleeding; [d] Total abdominal hysterectomy with bilateral salpingo-oophorectomy with pelvic lymph node dissection with para-aortic lymph node dissection; [e] Chemotherapy; [f] Right lower quadrant; [g] Total abdominal hysterectomy with bilateral salpingo-oophorectomy; [h] Radiation therapy; [i] Paclitaxel and carboplatin; [j] Total abdosminal hysterectomy; [k] Paclitaxel and cisplatin.

(https://www.ncbi.nlm.nih.gov/pubmed/?term=adenocarcinoma+adenomyosis) and retrieved a few relevant reports. After excluding cases that involved the endometrium, we had a total of 10 cases. The brief review of these cases is presented in Table 1 [7-15]. As shown in Table 1, abnormal uterine bleeding was reported in many cases. Only one case had no symptoms like our case. Seven of the 10 cases were at stage I at the time of diagnosis. The histology results were as follows: 5 endometrioid cases, 3 serous adenocarcinoma cases, and 2 clear cell cases.

Since 90% of the endometrial cancer patients present with vaginal bleeding, the disease tends to be diagnosed at a relatively early stage [16]. Contrary to this, EC-AIA could be associated with a delay in diagnosis, and often patients might be at a more advanced stage at presentation [17, 18]. Early diagnosis can be achieved by periodic follow-up using ultrasonography to detect any change in adenomyosis diagnosed at a reproductive age. In case of an intramyometrial mass increase in postmenopausal women, EC-AIA should be suspected in addition to sarcoma.

Conclusions

In summary, EC-AIA is very rare disease and should be considered as a different diagnosis from endometrial cancer cases with adenomyosis. EC-AIA should also be considered in patients with adenomyosis complaining of vaginal bleeding with an intact endometrium and in those with a history of adenomyosis at a reproductive age, regardless of the occurrence of vaginal bleeding. Periodic follow-up should be recommended in women diagnosed with adenomyosis at a reproductive age.

Ethics approval and consent to participate

This study was approved by the local Institutional Review Board (IRB) of the Kyung Hee University Hospital at Gangdong (IRB number: KHNMC 2020-05-030). We submitted an application for a waiver of the informed consent process which was granted to us.

Authors' contributions

Jong Min Lee and Seung Yeon Pyeon conceived and designed the case report; Seung Yeon Pyeon analyzed the data; Yun Jin Bang drafted the paper.

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Conflict of Interest

The authors declare no competing interests.

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References

[1] Lin X.L., Hai N., Zhang J., Han Z.Y., Yu J., Liu F., *et al.*: "Comparison between microwave ablation and radiofrequency ablation for treating symptomatic uterine adenomyosis". *Int. J. Hyperthermia*, 2020, *37*, 151-156.
[2] Leyendecker G., Wildt L.: "A new concept of endometriosis and adenomyosis: Tissue injury and repair (Tiar)". *Horm. Mol. Biol. Clin. Investig.,* 2011, *5*, 125-142.
[3] Tetikkurt S., Celik E., Tas H., Cay T., Isik S., Usta A.T.: "Coexistence of adenomyosis, adenocarcinoma, endometrial and myometrial lesions in resected uterine specimens". *Mol. Clin. Oncol.*, 2018, *9*, 231-237.
[4] Zhang Z., Yang B., Zhang W., Gao X., Zhao C., Zhang X., *et al.*: "Clinicopathological characteristics and survival outcomes of patients with coexistence of adenomyosis and endometrial carcinoma". *Int. J. Clin. Exp. Pathol.*, 2018, *11*, 956-962.
[5] Matsuo K., Cahoon S.S., Gualtieri M., Scannell C.A., Jung C.E., Takano T. *et al.*: "Significance of adenomyosis on tumor progression and survival outcome of endometrial cancer". *Ann. Surg. Oncol.*, 2014, *21*, 4246-4255.
[6] Colman H.I., Rosenthal A.H.: "Carcinoma developing in areas of adenomyosis". *Obstet. Gynecol.*, 1959, *14*, 342-348.
[7] Baba A., Yamazoe S., Dogru M., Ogawa M., Takamatsu K., Miyauchi J.: "Clear Cell Adenocarcinoma Arising from Adenomyotic Cyst: A case report and literature review". *J. Obstet. Gynaecol. Res.*, 2016, *42*, 217-223.
[8] Heo S.H., Lee K.H., Kim J.W., Jeong Y.Y.: "Unusual manifestation of endometrioid adenocarcinoma arising from subserosal cystic adenomyosis of the uterus: emphasis on mri and positron emission tomography Ct findings". *Br. J. Radiol.*, 2011, *84*, e210-e212.
[9] Hsu M.I., Chou S.Y., Lin S.E., Liang, S.J., Chiu H.C., Hsu C.S.: "Very early stage adenocarcinoma arising from adenomyosis in the uterus". *Taiwan J. Obstet. Gynecol.*, 2006, *45*, 346-349.
[10] Izadi-Mood N., Samadi N., Sarmadi S., Eftekhar Z.: "Papillary serous carcinoma arising from adenomyosis presenting as intramural leiomyoma". *Arch. Iran. Med.*, 2007, *10*, 258-260.
[11] Koshiyama M., Suzuki A., Ozawa M., Fujita K., Sakakibara A., Kawamura M., *et al.*: "Adenocarcinomas arising from uterine adenomyosis: A report of four cases". *Int. J. Gynecol. Pathol.*, 2002, *21*, 239-245.
[12] Liu C.H., Chang W.H., Liu W.M., Wang P.H.: "Serous carcinoma arising from adenomyosis". *Taiwan J. Obstet. Gynecol.*, 2017, *56*, 706-707.
[13] Lu B., Chen Q., Zhang X., Cheng L.: "Serous carcinoma arising from uterine adenomyosis/adenomyotic cyst of the cervical stump: A report of 3 cases". *Diagn. Pathol.*, 2016, *11*, 46.
[14] Mori M., Furusawa A., Kino N., Uno M., Ozaki Y., Yasugi T.: "Rare case of endometrioid adenocarcinoma arising from cystic adenomyosis". *J. Obstet. Gynaecol. Res.*, 2015, *41*, 324-328.
[15] Taga S., Sawada M., Nagai A., Yamamoto D., Hayase R.: "A case of endometrioid adenocarcinoma arising from adenomyosis". *Case Rep. Obstet. Gynecol.*, 2014, *2014*, 569295.
[16] Bagaria M., Shields E., Bakkum-Gamez J.N.: "Novel approaches to early detection of endometrial cancer". *Curr. Opin. Obstet. Gynecol.*, 2017, *29*, 40-46.
[17] Szegedi S., Koppan M., Varga T., Kovacs K., Tinneberg H.R., Bodis J.: "Endometrioid adenocarcinoma arising from adenomyosis: a case report". *Eur. J. Gynaecol. Oncol.*, 2016, *37*, 858-860.
[18] Kazandi M., Zeybek B., Terek M. C., Zekioglu O., Ozdemir N., Oztekin K.: "Grade 2 endometrioid adenocarcinoma arising from adenomyosis of the uterus: report of a case". *Eur. J. Gynaecol. Oncol.*, 2010, *31*, 719-721.

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