Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.41.006591

Clinicopathological Analysis of Sertoliform Endometrial Carcinoma of Uterus

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ARTICLE INFO

Received: January 11, 2022

Published: January 26, 2022

Citation: Yuan Yufen, Li Haimei. Clinicopathological Analysis of Sertoliform Endometrial Carcinoma of Uterus. Biomed J Sci & Tech Res 41(3)-2022. BJSTR. MS.ID.006591.

Keywords: Sertoliform Endometrial Carcinoma; Clinicopathological Characteristics; Uterus

Abbreviations: SEC: Sertoliform Endometrial Carcinoma; ER: Estrogen Receptor; PR: Progesterone Receptor; MSS: Microsatellite Stable State

ABSTRACT

Purposes: Sertoliform endometrial carcinoma (SEC) is a rare malignant tumor of uterine body. Because of its low incidence, this paper reports SEC in our hospital and reviews the previous eight cases in order to deepen the understanding of it.

Methods: Clinicopathological analysis was performed in 9 sertoliform endometrial carcinoma samples.

Results: A total of 9 cases were included in our study. Most patients have mild or moderate obesity, diabetes and hypertension. The patients were in the 41 to 83 age range. The main symptom was vaginal bleeding. The maximum diameter of the uterus's lesions was 0.7 to 9 cm. The cervix was involved in 3 of 9 cases. And for the case in our hospital, metastasis was found in both pelvic lymph nodes. Under the microscope, the tumor cells were mainly or partly arranged as cribriform or hollow tubules morphologically mimicked sertoli cells, and the cytoplasm was bright or light stained. And the interstitial reaction was not significant.

Conclusion: Sertoliform endometrial carcinoma (SEC) is occurred in perimenopausal and postmenopausal women without specific clinical symptoms. For the atypia and arrangement of tumor cells, it needs to be differentiated from sex cord stromal tumors and microglandular hyperplasia during biopsy or curettage. Although the histomorphology of the tumor cells were mild, some cases were clinically divided into stage III, so postoperative radiotherapy and chemotherapy were urgently needed to prevent postoperative recurrence and metastasis.

Introduction

Endometrial carcinoma is the most common malignant tumor of the uterus, which can be diagnosed by curettage or biopsy [1,2]. At present, there are some special subtypes of endometrial carcinoma, such as adenosis like endometrial carcinoma, whose morphological characteristics overlap with microglandular hyperplasia [3-6]. In addition. Other rare subtypes are also listed in the World Health Organization, but their understanding is still limited, such as sertoliform endometrial carcinoma [7]. In recent years, this kind of tumor has been reported more and more in the ovary [8-10]. However, less than 10 cases of sertoliform endometrial carcinoma have been reported in endometrium [3,11-14]. This paper reviews nine cases, including one in our hospital.

Methods

A retrospective analysis was made in 9 sertoliform endometrial carcinoma samples including clinical characteristics and

pathological features. The diagnostic criteria are as follows. Normal endometrial stroma disappeared, replaced by dense small glands, and neoplastic glands showed infiltrative growth pattern. The tumor cells were closely packed, which formed elongated tubules with basal antipldally oriented nuclei and central interdigitating cell processes composed of clear to fibrillar cytoplasm. The clinical characteristics were mainly clinical history, and the treatment was also described. The pathological features included histomorphology and immunohistochemistry.

Results

Clinical Data

Most of the patients were perimenopausal women with an average age of 59.33 years old (range from 41 to 83 years old). There were 9 cases in total (Table 1), of which 6 cases were in clinical stage I, 2 cases were in clinical stage II, 1 case was in clinical stage III. The main clinical symptom was irregular vaginal bleeding. Most patients had history of hypertension, diabetes and obesity.

Table 1: Clinical characteristics of 9 cases sertoliform endometrioid adenocarcinoma of the endometrium.

NO.	Age/ys	Stage	HT	Obese	DM	Vmax/cm	Symptom
1	41	Ia	/	/	/	2	IVB
2	62	II	+	+	/	7	PMB
3	44	Ia	+	+	+	5	IVB
4	60	Ia	+	+	+	5	PMB
5	71	Ia	+	+	-	4	PMB
6	83	Ia	+	+	+	1.7	Abdominal cervical smears
7	71	IIb	+	+	+	4.5	PMB
8	55	Ia	/	/	+	0.7	PMB
9	47	IIIc	-	+	-	9	IVB

Note: HT=hypertension; DM=diabetes; IVB= intermenstrual vaginal bleeding; PMB= Postmenopausal bleeding.

General and Microscopic View

General View: The tumor was mainly polypoid. The tumor of cervical involvement was not obvious or nodular (Table 2). The maximum diameter of the tumors range from 0.7cm to 9 cm. Similar to SEC on the ovary, SEC of the uterus was of low grade. It infiltrated into the myometrium and a few can invade the cervix stroma.

Table 2: General characteristics of 9 cases sertoliform endometrioid adenocarcinoma of the endometrium and/or cervix uteri.

NO.	Endometrium			Cervix uteria
	General	Other lesions	Number	
1	plaque	-	single	
2	exophytic tan mass	-	single	nodule
3	polyp	ovarian cyst	single	
4	polyp	leiomyomas	multiple	
5	polyp	-	single	
6	polyp	leiomyomas	single	unclear
7	polyp	-	single	
8	polyp	-	multiple	
9	polyp	bilateral pelvic lymph nodes +	single, diffuse	normal

Microscopic View (Figure 1): Under the microscope, the tumor cells were diffusely distributed, and there were closely packed small gland cavities, among which there were proliferative endometrial glands with normal stroma. The tumor cells are arranged in small, rigid tubes or cribriform shapes. Eosinophilic substance was found in the glandular cavity. The irregular gland cavities distributed in groups show rigid tubules, and the tumor cells were cubic or columnar with basal nuclei and centrally clear to fibrillar cytoplasm. The morphology of tumor cells in uterine body and cervical were similar. The tumor cells were embedded in the stroma of the uterine body, and tumor stromal reaction was not obvious. There was no inflammatory cell infiltration. The tumor cells are moderately heteromorphic, but they are highly invasive. In our case, the tumor cells invade the whole cervix and have bilateral pelvic lymph node metastasis. The tumor cells are moderately heteromorphic, but they are highly invasive. In our case, the tumor

cells invade the whole cervix and have bilateral pelvic lymph node metastasis. This inconsistency between biological behavior and morphology makes histological grading difficult. The pathological results also showed leiomyoma of uterus in case 4 and case 5.

Diagnostic Criteria: First, the tissue structure was hollow or cribriform tubules with high tension and hollowed out appearance. Most tubules are back-to-back and endless, forming a net among which scattered normal uterine mucosal glands can be seen. The tumor was small reticular or single glandular duct scattered in the muscle wall or cervical subepithelial stroma. Second, the tubule is lined with a layer of cuboidal or columnar cells, and the nucleus is close to the base, so a light stained cytoplasmic band without nuclear is formed inside the lumen. Third, homogeneous red staining was found in most lumens. Fourth, the tumor stromal reaction was absent or not obvious.

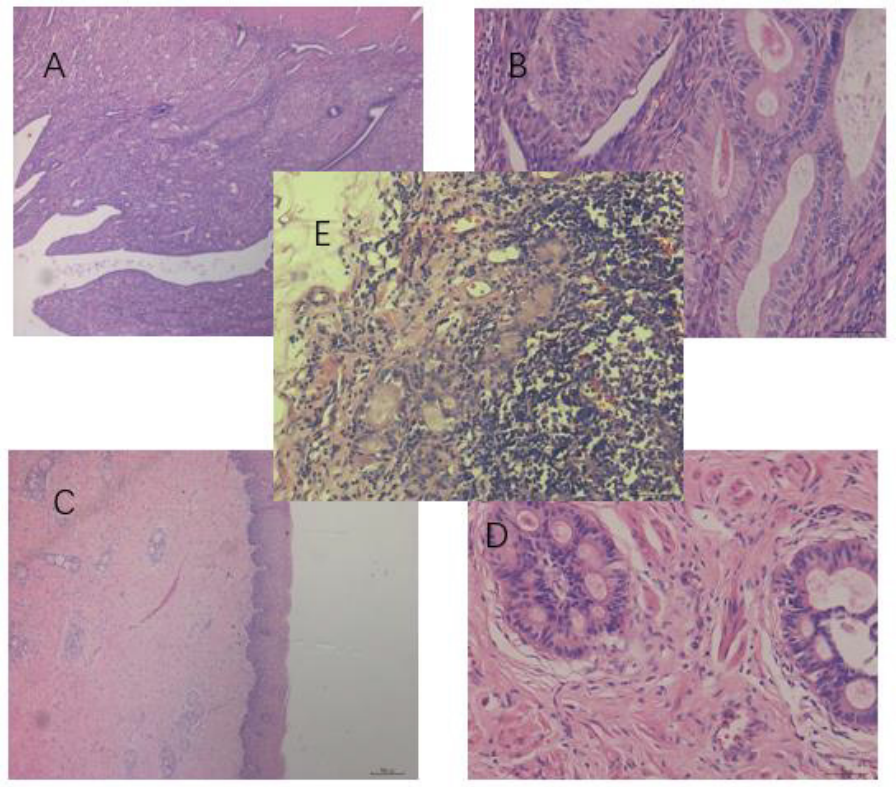

Figure 1: Microscopical examination. A. The endometrial tumor was mainly polypoid. The tumor cells were diffusely distributed, and there were closely packed small gland cavities, among which there were proliferative endometrial glands, HE, 40 x. B. The irregular gland cavities of uterine body distributed in groups show rigid tubules, and the tumor cells were cubic or columnar with basal nuclei and centrally clear to fibrillar cytoplasm. Eosinophilic substance was found in the glandular cavity, HE, 200 x. C. Tumor cells infiltrated into the stroma beneath the squamous epithelium of the cervix, HE, 40 x. D. Eosinophilic substances can also be seen in the tumor gonads of cervical stroma, HE, 200 x. E. The tumor gland beneath the capsule of the pelvic lymph node, HE, 200 x.

Immunohistochemistry

The tumor cells expressedAE1/AE3, vimentin, estrogen receptor(ER) and progesterone receptor(PR), while inhibin and p16 were negative in most cases. In case7, inhibin was positive in tumor cells.

Epithelial Markers (Figure 2): The endless connections of tumor gonadal ducts can be displayed by epithelial markers, such as EMA, AE1/AE3, CK8, etc. At the same time, Pax8 can also show this arrangement of neoplastic glands. And GATA3 was negative.

Mesenchymal Markers (Figure 3): The markers of sex cord stromal tumors were negative, including WT1, α- inhibin, MelanA, CD10, CD99, Calretinin. Myogenic markers were negative, such as desmin and h-caldesmon.

Biological Behavior Related Markers (Figure 4): The immunohistochemical results of case 9 showed that the positive rate of p53 was about 30%, ranging in strength, suggesting that p53 was wild-type. Microsatellite proteins including PMS2, MLH1, MSH2 and MSH6 were positive. Interestingly, CD10 is positively expressed among tumor cells, indicating that the endometrial stroma still exists in the uterus. The harmonious coexistence between neoplastic epithelium and normal stroma seems to contradict its highly invasive biological behavior.

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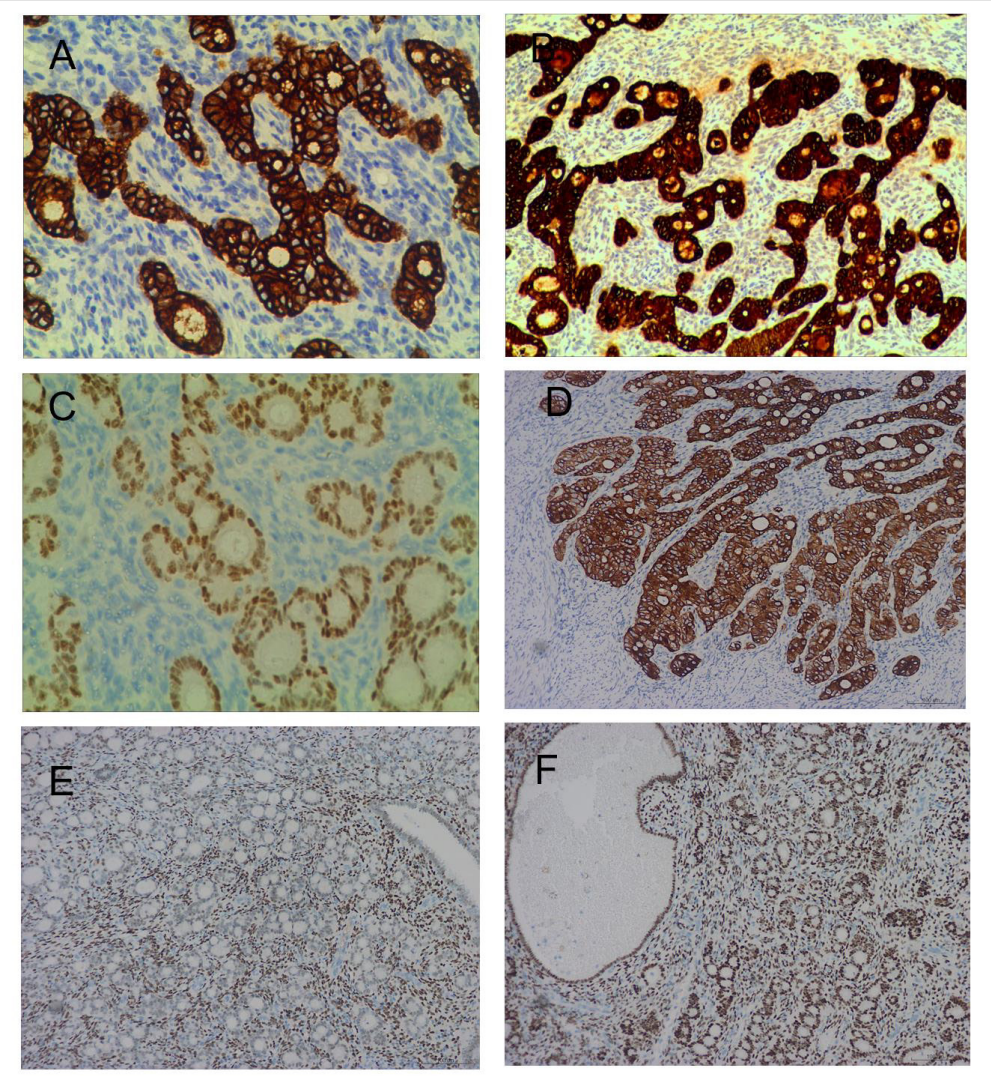

Figure 2: Immunophenotype of epithelial markers and hormone receptors. A. The expression pattern of CK8, 200 x. B. The expression pattern of EMA, 100 x. C. The expression pattern of PAX8, 200 x. D. The expression pattern of AE1/AE3, 100 x. E. The expression pattern of PR, 100 x. F. The expression pattern of ER, 100 x.

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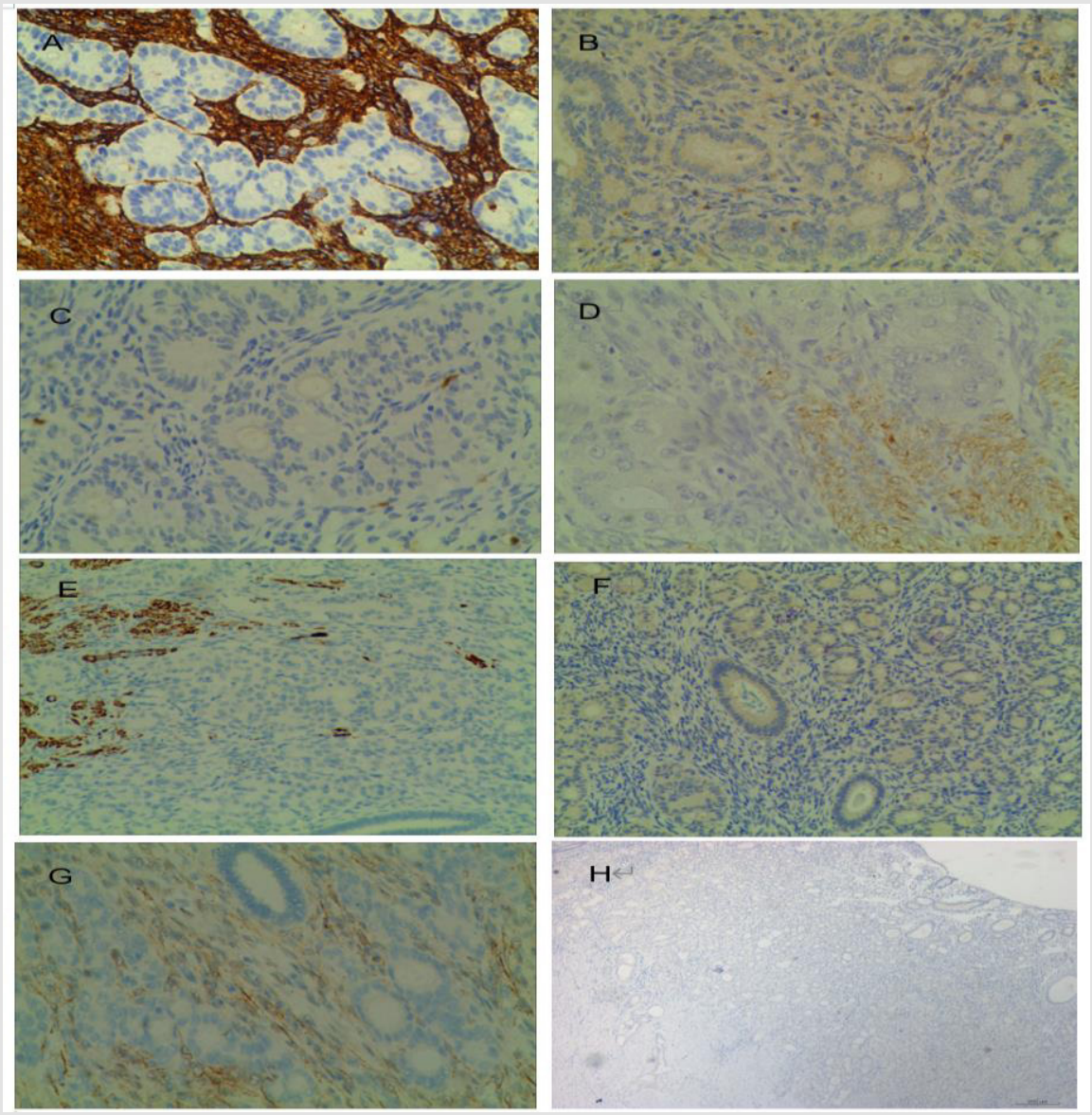

Figure 3: Immunophenotype of mesenchymal markers. A. The expression pattern of CD10, 200 x. B. The expression pattern of CD99, 200 x. C. The expression pattern of calretinin, 200 x. D. The expression pattern of Desmin, 200 x. E. The expression pattern of h-caldesmon 100 x. F. The expression pattern of MelanA, 100 x. G. The expression pattern of WT-1, 200 x. H. The expression pattern of inhibin, 40 x.

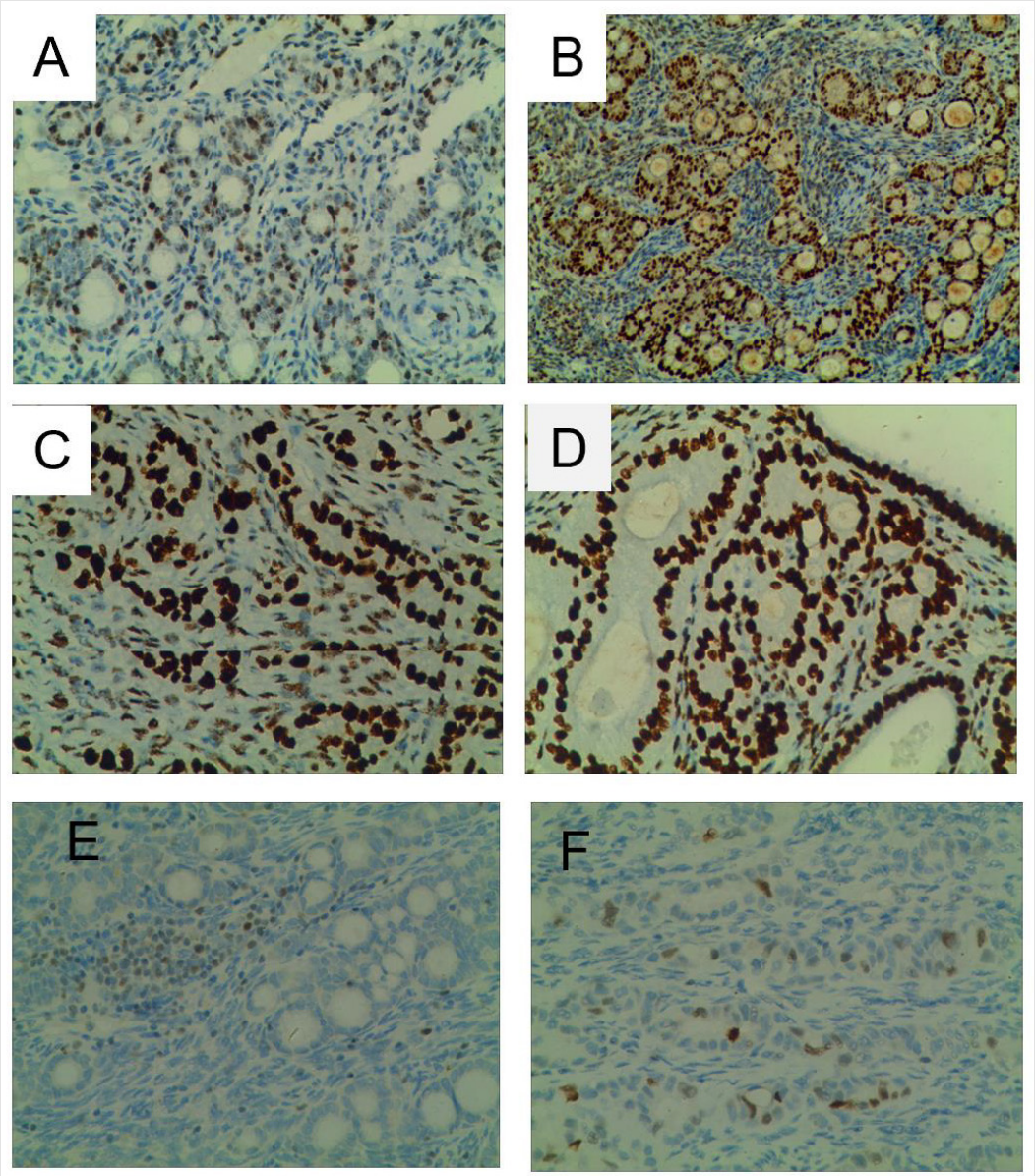

Figure 4: Immunophenotype of mismatch repair proteins and biological behavior related markers. A. The expression pattern of MLH1, 200 x. B. The expression pattern of PMS2, 200 x. C. The expression pattern of MSH2, 200 x. D. The expression pattern of MSH6, 200 x. E. The expression pattern of GATA3, 200 x. F. The expression pattern of P53, 200 x.

Treatment

After operation, radiotherapy and combined chemoradiotherapy were performed in case 7 and case 9 respectively, of which the clinical stages were stage II and stage III respectively. For case 8, no postoperative treatment was performed.

Follow-up

There was no recurrence or metastasis at 6 months (case 7), 10 months (case 8) and 22 months (case 9) after operation.

Discussion

Endometrial carcinoma is the most common malignant tumor of the uterine body [15]. The main clinical symptom was vaginal bleeding, which was not specific and had no significance for diagnosis. The main manifestation of the tumor was polypoid, and it is easy to miss diagnosis. Curettage biopsy is very important for the diagnosis [3,11-14]. Endometrial carcinoma may be accompanied by secretory changes, ciliary cell differentiation, squamous differentiation, mucinous differentiation, sex cord like

structure, etc. SEC is a rare endometrial carcinoma with sex cord differentiation [16]. Because SEC has the same immunophenotype as endometrial carcinoma, it is considered to be a special subtype of endometrial carcinoma [17,18]. Tumor cells of SEC coexist peacefully with the stroma of uterus. It is mild in shape but may have cervical stromal infiltration and even lymph node metastasis. Cervical involvement was found in three cases, one of which was metastasized to bilateral pelvic lymph nodes, and no recurrence or metastasis was found after comprehensive treatment. The inconsistency between morphology and biological behavior should be paid attention to by clinicians. To a certain extent, the absence of tumor stromal response and inflammatory cell response may protect tumor cells from immune surveillance, which may play an important role in the invasive behavior of tumor cells. Further exploration of tumor markers of the disease is conducive to the prevention and treatment of SEC.

Differential Diagnosis

Sertoli Cell Tumor: Most of them occurred in the ovary. Sertoli cell tumor is a mostly benign tumor of stromal origin other than epithelial origin, and it can be classified as well-differentiated, moderately differentiated, or poorly differentiated. When sertoli cell tumors appear as hollow tubules, its histological grade is highly differentiated, often accompanied by divergent nests of ledig cells. Immunohistochemical staining showed that α-inhibin, calretinin, CD99, CD56, SF-1, WT-1, MelanA were positive. EMA, PAX8 were negative. It rarely occurs in the uterine body, and cervical involvement and pelvic lymph node metastasis are more rare.

Uterine Tumors Resembling Ovarian Sex-Cord Tumor: Uterine tumors resembling ovarian sex-cord tumor is of unknown origin. It was shown as solid mass, adenoid structure or anastomotic cords. Some of them are resembling ovarian sex-cord tumors, such as granulosa cell tumor. Some cases showed different degrees of sex cord differentiation in immunohistochemistry. EMA, PAX8 were negative.

Invasive Adenocarcinoma of the Cervix: In rare cases, invasive cervical adenocarcinoma is morphologically similar to endometrioid adenocarcinoma. Immunohistochemical staining showed negative in ER and PR. For HPV-associated adenocarcinoma of the cervix, P16 was diffusely strong positive, while HPV-unrelated adenocarcinoma P16 was negative or focal positive.

Serous Carcinoma: The histological morphology of serous carcinomas (SEC) is not proportional to the histological structure. The neoplastic cells show severe atypia and may have glandular cribriform. P16 was diffusely strong positive and P53 is mutated. The histomorphology and structure of endometrioid adenocarcinoma are proportional. In other words,, the highly differentiated endometrioid carcinoma is adenoid, and the poorly differentiated endometrioid carcinoma is solid sheet. This case in our hospital is unique in that its histological structure is glandular, hollow tubule, or sieve like, and the tumor cell histological morphology is mild, but its biological behavior is highly aggressive.

Mesonephric Duct Tumor: Mesonephric duct tumors are mostly benign. It mainly occurred in the broad ligament, mesosalpinx and hilum of ovary. Immunohistochemistry showed that α-inhibin, calretinin, WT-1, FOXL-2 were positive. But EMA, ER, PR, GATA3, PAX8, SF1 were negative. When the tumor cells have obvious atypia, larger tumor volume and more mitosis, its invasiveness will be relatively strong. Mesonephric carcinoma is characterized by obvious atypia, large tumor volume and high mitotic count. Immunohistochemistry showed that TTF and GATA3 are positive in mesonephric carcinoma.

Characteristics of Molecular Biology

With the progress of molecular medicine, researchers have been studying tumors at the molecular level. In 2013, the tumor gene map research network (TCGA) studied 373 cases of endometrial carcinoma. Using the tumor samples of these cases, genomics, mRNA, miRNA sequencing, DNA methylation analysis, DNA copy number analysis and reverse phase protein array were analyzed. The microsatellite instability was analyzed by the following methods, four single nucleotide repeat sites and three dinucleotide repeat sites were marked. If the tumor DNA had no variation at the above sites, it was considered to be microsatellite stable state (MSS). If there is one or two site variation, it is considered to be low-level microsatellite instability (MSI-L). If 3 or more loci change, it is considered to be a highly microsatellite unstable state (MSI-H). Combined with mutation pedigree, microsatellite instability (MSI) and somatic copy number changes (scans), TCGA proposed to divide endometrial cancer into four categories. DNA polymerase ε Pole ultramutated, MSI, low copy number, high copy number.

Prognostic Characteristics

The prognosis is favorable in there follow-up cases [13,14]. This is consistent with the prognosis of common endometrioid adenocarcinoma. At present, the treatment of SEC is based on its clinical stage, and the treatment principle refers to the same stage of endometrioid adenocarcinoma. Whether postoperative treatment is necessary needs to be supported by more clinical data. Most patients had history of hypertension, diabetes and obesity. Whether obesity, diabetes and hypertension are incidental, or whether they have a causal relationship with tumorigenesis remains unknown [15-18]. The relationship between SEC and the concomitant diseases needs to be further explored. In a word, due to the small number of cases and insufficient understanding of its clinicopathological features and pathogenesis, it is necessary to improve the understanding of the disease through large sample and long-term follow-up.

Conclusion

Sertoliform endometrial carcinoma (SEC) is occurred in perimenopausal and postmenopausal women without specific clinical symptoms. For the atypia and arrangement of tumor cells, it needs to be differentiated from sex cord stromal tumors and microglandular hyperplasia during biopsy or curettage. Although the histomorphology of the tumor cells were mild, some cases were clinically divided into stage III, so postoperative radiotherapy and chemotherapy were urgently needed to prevent postoperative recurrence and metastasis.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributor

- Author contributions of Yuan Yufen are drafting the work and writing review & editing
- Author contribution of Li Haimei is writing original draft.

Ethics

This is an observational study. The Ethics Committee of Anyang Tumor Hospital has confirmed that no ethical approval is required.

Funding

No.

Instructions for the Contributors

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.41.006591

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