Invasive Stratified Mucin-Producing Carcinoma (ISMC) of The Uterine Cervix: A Clinicopathological Study of 8 Cases

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Research

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Abstract

Invasive stratified mucin-producing carcinoma (ISMC) is a rare gynecologic malignancy. Previous studies suggested that ISMC was a morphologic variant of invasive cervical adenocarcinoma. The clinicopathologic features and prognosis of eight cases of ISMC are presented. Clinical symptoms and imaging were atypical. Four cases were pure ISMCs, and four cases were ISMCs mixed with usual-type endocervical adenocarcinomas. The depths of stromal invasion were more than half (5/8), with approximate full-thickness in one case, and there was vascular invasion (5/8), neutral invasion (3/8), uterine segment involvement (3/8), and parametrial involvement (1/8). One of the patients underwent vaginal cuff surgery. Lymph node metastasis was seen in two patients (2/8). All cases were diffusely positive for p16 and high Ki67 expression. These cases had high-risk HPV16,18, 58 infection. All patients were alive after surgery and adjuvant therapy during the 8- to 21-month follow-up, and only one developed vaginal wall recurrence at 15 months. The present data and those obtained from the literature suggest that ISMC is an invasive endocervical adenocarcinoma with high-risk HPV infection, mainly HPV18, and has a risk of recurrence and metastasis.

Introduction

Traditionally, high-grade squamous intraepithelial lesions (H-SILs) and adenocarcinoma in situ (AIS) are precursor lesions for invasive cervical carcinoma. In 2000, *Park et al* [1] first proposed SMILE, a distinct form of H-SIL and AIS. SMILE is a rare columnar cell cervical neoplasm that is characterized by stratified, immature epithelial cells displaying varying quantities of intracytoplasmic mucin throughout the majority of the lesional epithelium at the transformation zone by transdifferentiation [1]. Similar to H-SIL and AIS, SMILE is associated with high-risk HPV infection [2, 3, 5–7]. In 2014, the World Health Organization (WHO) classification described SMILE as a precursor for cervical carcinoma, a variant pattern of AIS [3, 4]. In 2016, Lastra et al [3] identified a distinct form of invasive cervical carcinoma with morphologic features identical to those in SMILE and proposed the invasive form of SMILE to be “invasive stratified mucin-producing carcinoma”. The clinicopathologic features and prognostic information regarding ISMC are limited in the literature. In this report, we present a case series of ISMC and review the literature.

Materials And Methods

A total of eight cases of ISMC were reviewed at the Pathology Department of West China Second University Hospital from 2019 to 2020. In all cases, four cases were pure ISMCs, and four cases coexisted with ISMCs and usual-type endocervical adenocarcinomas. Clinical information and follow-up data were obtained from the patients’ electronic records. The pathological parameters evaluated were tumor size, depth of stromal invasion, vascular invasion, neutral invasion, uterine segment and parametrial involvement and lymph node metastasis. Hematoxylin and eosin-stained slides were reviewed by specialist gynecologic pathologists. Immunohistochemistry staining was performed with p16, p63, CK5/6, CK8, CK18, CEA and Ki67 in patients. HPV type detection was performed in eight cases, including 13 high-risk types (types 16,18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82).

Results

Clinical Features

The clinical features of eight cases of ISMC are presented in Table 1. The patients’ ages ranged from 40 to 51 years (mean 48 years). According to available medical records, none of the patients had a previous history of

malignancy. All of them had offspring, and one of them had gone through menopause (case 7). All patients presented with vaginal bleeding. Elevated serum SCC levels were noted in one patient (case 7). Regarding the physical examination, eight patients had a cervical mass at differing degrees, and the mass was characterized by erosion, poor crisp and positive blood contact. Imaging studies with ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) revealed that there was soft tissue in the cervix, and no enlarged lymph nodes were found in the pelvic cavity. A thin-prep cytology test showed HSIL in four patients, and the other four patients were diagnosed with carcinoma by cervical biopsy directly. The colposcopy biopsy was diagnosed as carcinoma, of which two were mucinous adenocarcinomas, three were squamous cell carcinomas, one was adenocarcinoma, one was ISMC, and one was ISMC mixed with usual-type endocervical adenocarcinomas. In the postoperative diagnosis, four cases were pure ISMCs, and four cases were ISMCs mixed with usual-type endocervical adenocarcinomas. The patients' FIGO stages ranged from IB1 to IIB.

Table 1
The clinical features of eight cases of ISMC

Case No.	Age (Years)	Symptoms of the lesion	Thin-prep cytology test	Preoperative diagnosis	Postoperative diagnosis	Stage	Treatment	Follow-up
1	40	Vag. bleeding	NA	ISMC	ISMC	FIGO IIB	RH + BSO + PL + PLNS,CRT	Vaginal recurrence (15 months) treated with RT, Alive 21 months
2	50	Vag. bleeding after sexual intercourse	NA	MUC	ISMC + UEA	FIGO IB1	RH + BSO + PL + PLNS,CRT	Alive 18 months
3	49	Vag. bleeding after sexual intercourse	HSIL	MUC	ISMC	FIGO IIA1	RH + BSO + PL + PLNS,CRT	Alive 13 months
4	48	Vag. bleeding	HSIL	ISMC + UEA	ISMC + UEA	FIGO IB2	RH + BSO + PL + PLNS,CT	Alive 13 months
5	48	Vag. bleeding after sexual intercourse	NA	SCC	ISMC + UEA	FIGO IB1	RH + BSO + PL + PLNS	Alive 10 months
6	47	Vag. bleeding	HSIL	SCC	ISMC	IB2	RH + BSO + PL + PLNS,CRT	Alive10 months
7	51	Vag. bleeding after sexual intercourse	HSIL	Ade	ISMC + UEA	IB1	RH + BSO + PL + PLNS,CRT	Alive 9 months
8	51	Vag. bleeding after sexual intercourse	NA	SCC	ISMC	FIGO IB2	RH + BSO + PL + PLNS	Alive 8 months

• Vag: vaginal, NA: not applicable, HSIL: high-grade squamous intraepithelial lesion, ISMC: invasive stratified mucin-producing carcinoma, MUC: mucinous adenocarcinoma, SCC: squamous cell carcinoma, Ade: adenocarcinoma, UEA: usual-type endocervical adenocarcinomas, RH: radical hysterectomy, BSO: bilateral salpingo-oophorectomy, PL: pelvic lymph node dissection, PLNS: para-aortic node sampling, CT: chemotherapy, CRT: chemoradiotherapy.

Pathology Findings

The pathology findings of eight patients are summarized in Table 2. The tumor sizes ranged from 25 to 50 mm (mean 33 mm). The growth patterns of our cases were endophytic (4/8), exogenous (3/8), and neck (1/8). The depth of stromal invasion ranged from 1/3 to 1. Five patients' depths of stromal invasion were more than half, and one of them was approximately full-thickness. The other three patients' depths of stromal invasion were less than half. Vascular invasion was seen in five patients (5/8), and neutral invasion was seen in three patients (3/8). Uterine segment involvement was present in three patients (3/8), parametrial involvement was present in one patient (1/8), and one of the patients had vaginal cuff involvement during surgery. Lymph node metastasis was seen in two patients (2/8), one patient had metastasis to the left obturator lymph nodes, and another patient had metastasis to the bilateral pelvic lymph nodes and para-aortic lymph nodes.

Table 2
The pathology findings of eight patients

Case No.	Tumor size (mm)	Growth pattern	Depth of stromal invasion	Vascular invasion	Neutral invasion	Uterine segment and parametrial involvement	Lymph node metastasis
1	40	Endophytic type	1/3 ~ 1	Yes	Yes	Involving cervical junction, vaginal fornix and vaginal cuff	No
2	30	Endophytic type	< 1/2	Yes	No	No	No
3	35	Exogenous type	> 1/2	Yes	No	No	Left obturator lymph nodes
4	25	Neck type	< 1/2	No	No	No	No
5	30	Endophytic type	< 1/2	No	No	No	No
6	25	Endophytic type	> 1/2	Yes	Yes	Involving cervical junction	No
7	30	Exogenous type	> 1/2	Yes	Yes	Involving vaginal fornix and right parametrial tissues	Bilateral pelvic lymph nodes and para-aortic lymph nodes
8	50	Exogenous type	> 1/2	No	No	No	No

Microscopical Examination

All ISMC cases showed nests of stratified columnar cells with intracytoplasmic mucin, with round slightly irregular palisading infiltrating cervical stroma (Fig. 1). Intracytoplasmic mucins were seen throughout the nests in variable amounts. The amount of mucus in cells varied from case to case or from area to area. Our ISMC cases showed infiltrative growth of the tumor cell nest with a finger-like pattern of invasion, accompanied by a strong peritumoral inflammatory response with a predominance of neutrophils (Fig. 1A, B, E, F). Four cases were pure ISMCs, and four cases were ISMCs mixed with usual-type endocervical adenocarcinomas. The mixed cases showed a glandular growth pattern (Fig. 1C-D).

(Fig. 1) (A) (B) (C) (D) (E) (F)

Immunohistochemistry

All ISMCs were diffusely positive for p16 and showed high Ki67 expression; the Ki-67 positive index was 75–98%. All except one ISMC that was not tested were p63 negative. Immunohistochemistry staining of ck8, ck18, and CEA was performed in seven ISMCs: six ISMCs were focally and weakly positive, and one was strongly and diffusely positive. Seven ISMCs were negative or weakly positive for CK5/6, and one was not tested.

Human Papillomavirus Type Detection

The HPV type was detected in eight patients. All patients were positive for HPV. HPV16 and HPV18 accounted for three (3/8) and seven (7/8) patients, respectively. Two patients were positive for HPV 58. Among eight patients, three tested positive for HPV16 and HPV18, one was positive for HPV18 and HPV58, three were positive only for HPV18, and one was positive for HPV58.

Management and Follow-up

Eight patients underwent radical hysterectomy with bilateral salpingo-oophorectomy, pelvic lymph node dissection and para-aortic node sampling. Four patients underwent laparoscopy, and the others underwent abdominal surgery. Only one patient received three cycles of preoperative chemotherapy because of the large cervical mass. Six patients were treated with radiotherapy and/or chemotherapy after surgery, two

remaining patients did not receive any further treatment. Follow-up time ranged from 8 to 21 months (mean 13 months). To date, all patients are alive, and only one patient developed vaginal wall recurrence at 15 months. Even though she has undergone nine radiotherapy treatments, she continues to have difficulty urinating. She is waiting to be evaluated for reoperation.

Discussion

ISMC is a recently recognized distinct type of invasive cervical adenocarcinoma [3, 8], which was described by Lastra et al [3] as a morphologic variant of endocervical adenocarcinoma. SMILE is believed to be a putative precursor of ISMC because of their similar morphology. ISMC is an uncommon malignant cervical tumor. The mean age of ISMC among our cases was 48 years (range 40–51 years). As reported by Horn et al [7], the average age of ISMC is similar to that of invasive squamous cell and other histologic subtypes of invasive cervical adenocarcinoma. The symptoms of ISMC have no specific characteristics that distinguish them from usual invasive cervical carcinoma [9]. The ISMCs of our cases manifested as vaginal bleeding. However, owing to the ignorance of SMILE and ISMC, the thin-prep cytology test resulted in a misdiagnosis, namely, H-SIL, among our four cases, and the preoperative colposcopy biopsy was misdiagnosed as mucinous adenocarcinoma and squamous cell carcinoma in our five cases. Therefore, routine histological sections and immunohistochemical staining of ISMCs are particularly important for diagnosis.

ISMC is recognized as a mucinous subtype of HPV-associated adenocarcinoma by the International Endocervical Adenocarcinoma Criteria and Classification (IECC) system [9]. Similar to other histologic subtypes of cervical adenocarcinomas [7], HPV high-risk DNA can be detected in ISMCs [7–10]. The analysis of our cases demonstrated high-risk HPV in all informative cases and p16 overexpression in all tumors, supporting the hypothesis that high-risk HPV is associated with tumor development, mainly HPV 18. Immunohistochemical staining showed that most tumor cells were positive for p16, ck8, ck18, and CEA expression; had a high Ki-67 index; and were negative for

CK5/6 and p63. IMP3 is a member of the insulin-like growth factor protein family and is a useful marker for several carcinomas [11]. Onishi [8] reported that IMP3 was more strongly and diffusely positive in invasive cervical adenocarcinoma than in intraepithelial lesions. IMP3 expression may be helpful in the differential diagnosis of ISMC and SMILE.

In general, most ISMCs show a pure stratified mucin-producing histology, whereas mixed cases are also reported to be accompanied by adenocarcinoma of the usual, endometroid or colloidal type or squamous cell carcinoma [3,7–8,12–13]. Among our cases, four were pure ISMCs, and four were ISMCs mixed with usual-type endocervical adenocarcinomas. The five cases were preoperatively misdiagnosed as mucinous adenocarcinoma and squamous cell carcinoma. As described by Stolnicu et al [12], ISMC can display a wide morphologic spectrum that can impart an ambiguous appearance and make it difficult to classify the tumor, especially to distinguish it from traditional poorly differentiated HPV-associated usual-type and mucinous-type adenocarcinoma.

There was a wide range of tumor sizes, with a mean size of 33 mm (ranging from 25–50 mm) among our cases. In the presence of the endophytic type and neck type, most of the cases were diagnosed with tumors > 20 mm. Typically, ISMC shows a cauliflower-like, papillary and ulcerous appearance. In our cases, most ISMCs had a depth of stromal invasion of more than half (5/8), vascular invasion (5/8), neutral invasion (3/8), uterine segment involvement (3/8), parametrial involvement (1/8), and lymph node metastasis (2/8). Based on the pathology findings of the ISMCs, ISMC may be more invasive in the stroma and vasculature.

The clinical stage of cervical carcinoma is of great significance to the prognosis and treatment. The higher the clinical stage is, the greater the risk of death will be among patients with cervical cancer. Survival in cervical carcinoma depends on stage, with 99% five-year survival for stage IA1, 65% for IIB and 43% for IIIB disease [14]. The presence of pelvic/para-aortal lymph node metastases, local extension of the disease and tumor size are also well-established prognostic factors of cervical carcinomas [16–17]. The mean tumor size of six recurrent patients was 5.7 cm (range 4.1 to 6.4 cm), as provided in published reports [3, 7]. Five patients showed pelvic lymph node metastases reported by Horn et al [7]. During the follow-up period of 6 weeks to 28 months, all of them developed pelvic recurrence. In our study, one patient developed vaginal recurrence, and the depth of stromal invasion of the tumor was full-thickness, accompanied by vascular and neutral invasion, cervical junction, vaginal fornix and vaginal cuff infiltration.

Several studies have suggested that ISMC is potentially more aggressive, with worse outcomes than usual-type endocervical adenocarcinomas [3, 7, 15] and with a substantial risk of distant metastatic disease, especially to the lung [7]. All five patients with ISMCs reported by Horn et al [7] showed pelvic recurrence within 6 weeks to 12 months during follow-up, and four patients had died. In the report of Lastra et al [3], two of the five patients with ISMCs presented with parametrial involvement and histologically proven pulmonary metastases after 9 months and 36 months, respectively. One patient developed widespread peritoneal disease at the time of diagnosis and died 1.5 months later. Nonetheless, all three patients with ISMCs in the report of Onishi et al [8] were alive without recurrence during a mean follow-up of 59.3 months. Three patients reported by Lei et al [9] were alive with no recurrence from 19 to 27 months of follow-up. Our eight patients were alive from 8 to 21 months of follow-up, and only one developed vaginal wall recurrence at 15 months. Until this study, there were 17 cases reported [3, 7–9, 13]; the addition of the 8 cases in our study brings the total to 25 cases. Eight of the 25 patients with information developed recurrent disease from 6 weeks to 36 months, and four patients developed distant metastases.

Conclusions

In conclusion, ISMC is a distinct subtype of invasive endocervical adenocarcinoma with high-risk HPV infection, mainly HPV18. To avoid misdiagnosis, histological sections and immunohistochemical staining of ISMCs are particularly important. Regardless of the tumor size and tumor clinical stage, ISMC may represent an aggressive tumor with a risk of recurrence and metastasis. To better understand the clinicopathological features and prognosis of ISMC, more large-sample studies and more detailed data are needed.

Abbreviations

SMILE: stratified mucin-producing intraepithelial lesion

ISMC: invasive stratified mucin-producing carcinoma

FIGO: Federation of Gynecology and Obstetrics

H-SIL: high-grade squamous intraepithelial lesions

AIS: adenocarcinoma in situ

WHO: World Health Organization

MRI: Magnetic Resonance Imaging

CT: computerized tomography

HPV: human papilloma virus

Ki-67: Ki-67 protein

CEA: carcino-embryonic antigen

P63: protein 63

P16: protein 16

CK5/6: cytokeratin 5/6 antigen

CK8: cytokeratin 8 antigen

CK18: cytokeratin 18 antigen

IECC: International Endocervical Adenocarcinoma Criteria and Classification

IMP3: Insulin-like growth factor II mRNA binding protein antibody 3

Declarations

Ethics approval and consent to participate.

All tissue samples form patients were collected and protocols were performed according to the procedures approved by the Research Ethics Committee of Sichuan University. All patients provided informed consent.

Consent for publication

Not applicable

Avaliablity of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors were involved in drafting and revising the manuscript, and all authors read and approved the final manuscript.

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Figures

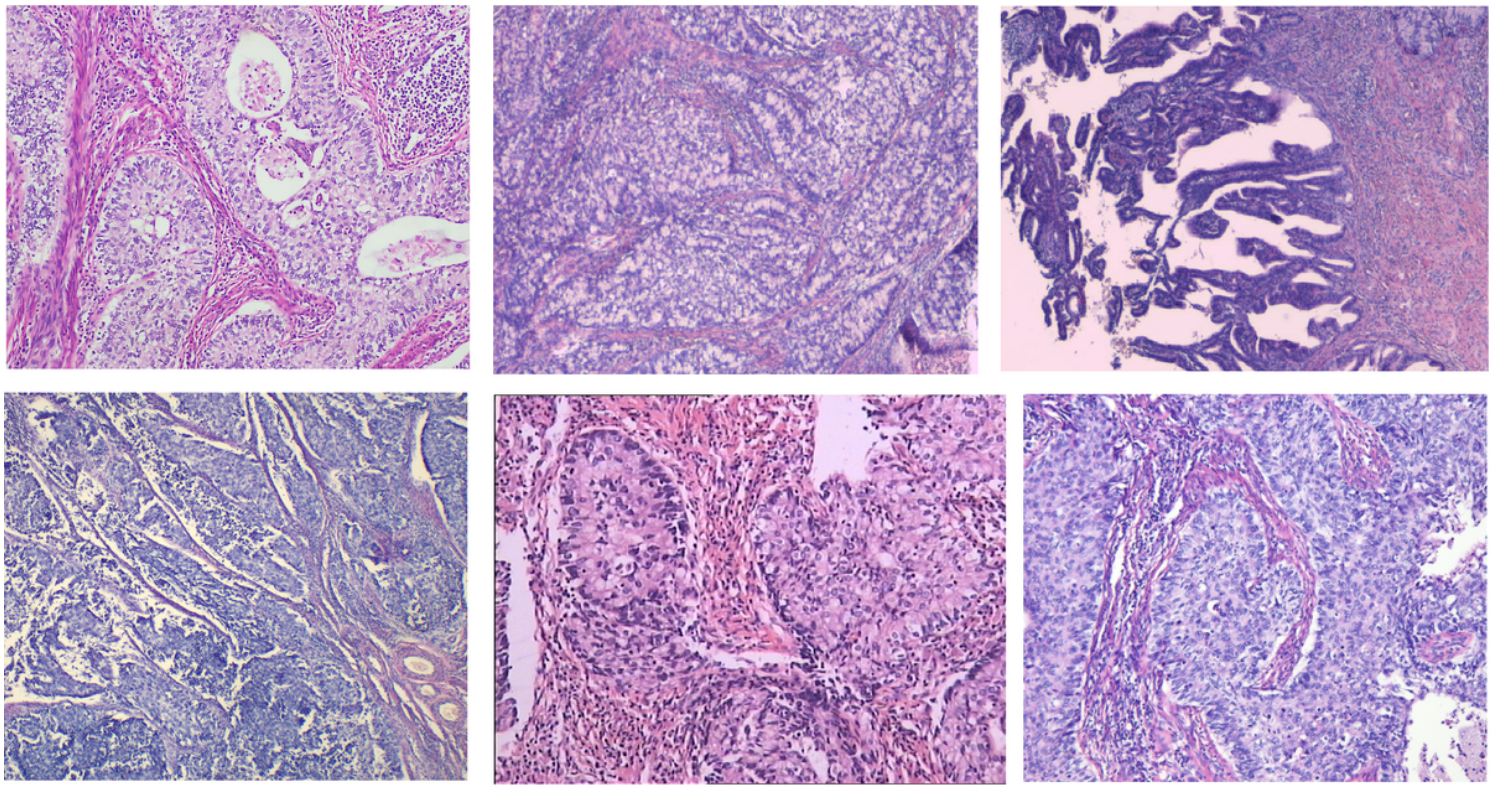

Figure 1

A-F: ISMCs showed nests of stratified columnar cells with variable amounts of intracytoplasmic mucin, with round slightly irregular palisading infiltrating cervical stroma. A, B showed ISMC cells with strong peritumoral inflammatory response and finger-like pattern of invasion. C, D showed glandular morphology, representing cervical adenocarcinoma of the usual type, mixed with ISMCs. (A-D: H&E x 100, E-F: H&E x 200)

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