Journal of Cancer Research and Clinical Oncology (2019) 145:2573–2582
https://doi.org/10.1007/s00432-019-02991-3

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Invasive stratified mucin-producing carcinoma (i-SMILE) of the uterine cervix: report of a case series and review of the literature indicating poor prognostic subtype of cervical adenocarcinoma

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Received: 29 January 2019 / Accepted: 5 March 2019 / Published online: 5 August 2019

Abstract

Purpose Invasive stratified mucin-producing carcinoma (i-SMILE) represents a recently recognized subtype of cervical adenocarcinoma (AC) developing in a background of a stratified mucin-producing intraepithelial lesion (SMILE). Clinical and prognostic data on i-SMILE are limited.

Methods We report a series of five cases with histopathological, immunohistochemical (p16) and PCR analyses. The cases as well as the patients previously published in the literature were reviewed for follow-up information.

Results Thirteen cases were identified. The mean age of 47.1 years (range 34–66) was not different from the usual type of cervical AC. 10/13 cases presented with tumors > 2 cm and a polypoid-exophytic appearance. Regardless of tumor size and stage of the disease, 7 out of 11 patients developed recurrent disease after a mean of 7.8 months (range 6 weeks–36 months). Five patients developed distant metastases (three of them in the lungs). Five out of the 11 informative cases died of the disease. All reported cases were positive for high-risk HPV (mainly HPV type 18) and associated with p16-overexpression.

Conclusion i-SMILE represent a distinct subtype of invasive endocervical AC, associated high-risk HPV infection and strong p16-overexpression. Clinically, i-SMILE may represent an aggressive tumor with early recurrent disease and substantial risk of distant metastatic disease, especially to the lungs.

Keywords Cervix · Cancer · TMMR · SMILE · Invasive · Stratified mucin-producing carcinoma · Adenocarcinoma · p16 · Prognosis · HPV

Introduction

Traditionally, precursor lesions of invasive cervical carcinoma are classified into high-grade squamous intraepithelial lesions (H-SIL, syn. CIN 3) and adenocarcinoma in situ (AIS). In 2000, a distinct form of an intraepithelial lesion was described (Park et al. 2000), namely a stratified epithelium with intracytoplasmic mucin vacuoles and immature nuclei which was termed "stratified mucin-producing intraepithelial lesion" (SMILE). In 2014, this lesion was incorporated in the WHO classification in addition to the well-recognized precursors for cervical carcinoma, H-SIL and AIS. In analogy to H-SIL and AIS, SMILE has been shown to be associated with high-risk HPV infections (Boyle and McCluggage 2015; Sano et al. 2014). In 2016, a distinct form of invasive cervical adenocarcinoma (AC) was described in association with SMILE and termed invasive stratified mucin-producing carcinoma (ISMC or i-SMILE; Lastra et al. 2016; Onishi et al. 2016). Clinical

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00432-019-02991-3) contains supplementary material, which is available to authorized users.

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and prognostic information are very limited for this particular subtype of cervical AC. In this report, we describe a case series of i-SMILE and review the literature regarding prognostic information.

Materials and methods

The cases examined in this study were retrieved by three methods. Two consecutive, recently diagnosed cases of i-SMILE were included. Three cases resulted from a retrospective, not yet published study for the re-classification of 30 adenocarcinomas from our hospital. Additionally, clinical and prognostic information was obtained from the literature of the published cases of i-SMILE. Patients with microinvasive disease, according to FIGO stage IA disease, were excluded from the analyses.

Analyses of the cases from Leipzig University Hospital

The retrospective cases retrieved as a result of the above-mentioned re-classification study were treated by radical hysterectomy Piver et al. (1974) and systematic pelvic lymphadenectomy. The two recent cases were surgically treated by total mesometrial resection (TMMR) and therapeutic lymphadenectomy (t-LNE; Höckel et al. 2012).

The pathological examination was performed in a standardized manner (Kurman and Amin 1999) for all cases. All tumors were (re-)classified according to the WHO classification and the recently described features for i-SMILE (Wilbur et al. 2014; Lastra et al. 2016; Onishi et al. 2016) as well as (re-)staged based on the TNM classification (Brierley et al. 2017).

Furthermore, immunohistochemical analyses for the expression of p16 and PCR-analyses for the detection of high-risk HPV were performed.

DNA extraction

Total DNA was isolated from three FFPE tissue sections (10 µm thick) using MagCore®Genomic DNA Tissue Kit and MagCore® Nucleic acid extractor according to the manufacturer's protocol (RBC Bioscience corp., Taipei City, Taiwan). DNA was eluted in 60 µl Tris–HCl. DNA concentration was assessed using Nanodrop 1000 (Thermo-Scientific, Wilmington, Germany).

LCD array

For human papilloma virus DNA amplification and identification, HPV^{Type}3.5 LCD-Array-Kit was used according to the manufacturer`s protocol (Chipron, Berlin, Germany).

Fig. 1 Radiological imaging and pathologic findings of i-SMILE and its recurrence. **a, b** MRI scans representing a huge polypous-exophytic tumor of the uterine cervix with mesometrial infiltration (arrow); **c** TMMR specimen from the dorsal site with a barrel-shaped bulky tumor without infiltration of the uterine serosa; **d–f** mucinous adenocarcinoma with i-SMILE-features (**d**), surrounded by dense eosiniphilic infiltrate (**e**) with strong immunostaining for p16 (**f**); **g** histologic picture of lymph node involvement by i-SMILE, focally with peritumoral eosinophils (X) within the lympho-nodal stroma; **h** pelvic recurrency: MRI scan representing a central tumor in close connection to the urinary bladder and the rectal wall; **i–k** pathologic findings within the LEER specimen: sagittal cut of the resection specimen (**i**) showing the central and supravaginal recurrent tumor, histopathologically with infiltration of the rectum (**j**), growing in the direction to the pelvic side wall without the infiltration of the pelvic fascia (arrow) and the resection margin of the pelvic side wall which is marked by black ink (**k**); **l** histologic picture showing cutaneous involvement at the inguinal recurrency; **m** detection of HPV high-risk infection by HPV-type 18 and 39

40 and 200 ng of total DNA was used from each sample for PCR amplification with My11/09 and 125 primer mix. PCR products were analyzed using Qiaxcel system (Qiagen, Hilden, Germany). 5 µl of each PCR product was hybridized on LCD chip. Dry slide was analyzed with Chipron PF7250 slide scanner (Chipron, Berlin, Germany).

Follow-up information was obtained from the medical charts. Written informed consent was obtained from all in-house patients. The study was approved by the Institutional Review Board.

Evaluation of the previously published cases

All published studies of i-SMILE were re-evaluated for clinical presentation of the patients, treatment approach and prognostic information (Park et al. 2013; Boyle and McCluggage 2015; Lastra et al. 2016; Onishi et al. 2016; Stolnicu et al. 2018).

Results

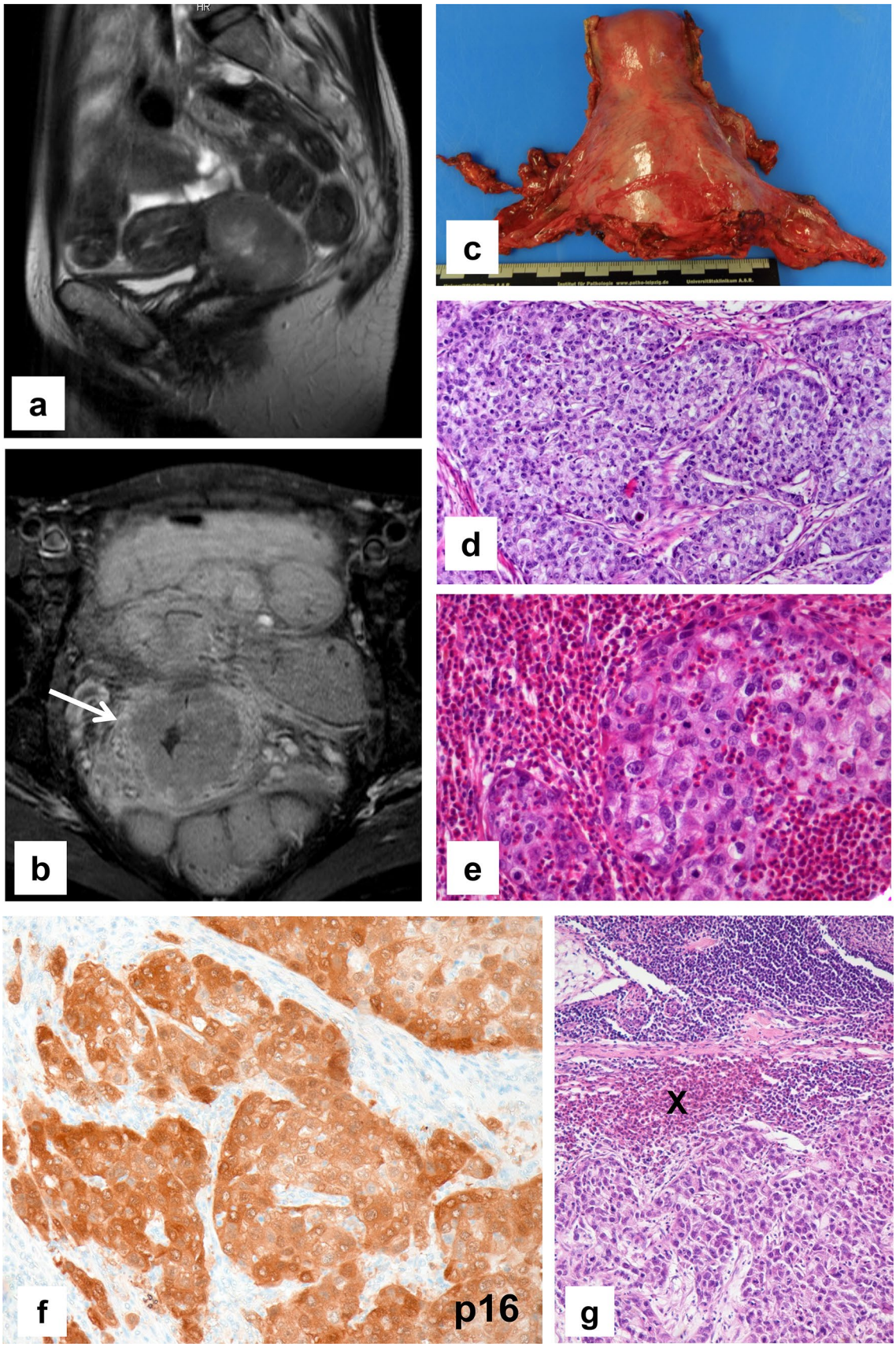
Cases from Leipzig University Hospital

Three cases of i-SMILE were identified by histopathological re-classification of 30 adenocarcinomas, representing a frequency of 10%.

The presenting symptoms were atypical Pap smear, vaginal discharge and/or bleeding, and two patients showed bleeding after sexual intercourse.

All patients received complete histopathological tumor resection.

Four out of five patients received adjuvant treatment by combined radiation and/or chemotherapy. One patient declined adjuvant therapy.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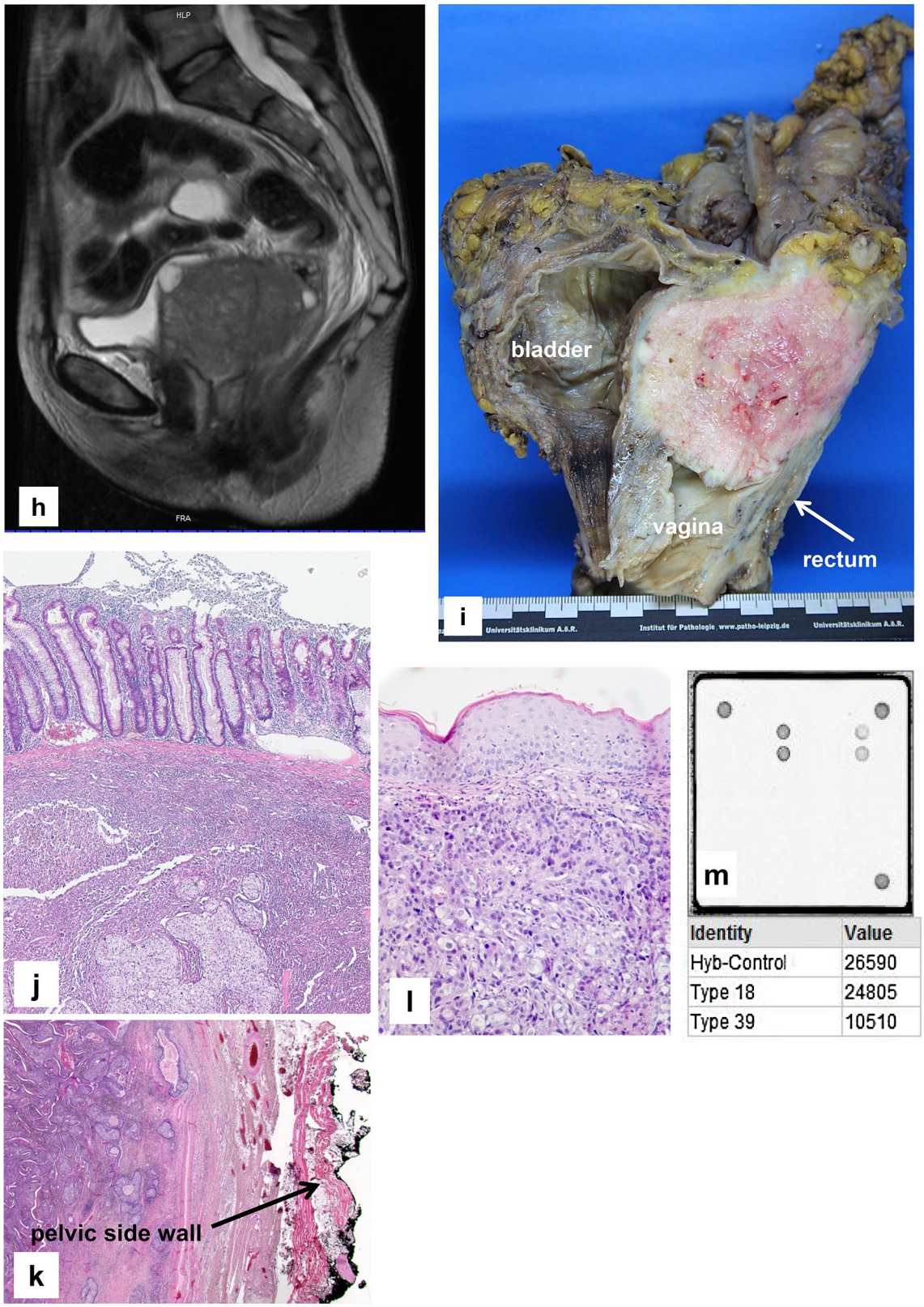


Fig. 1 (continued)

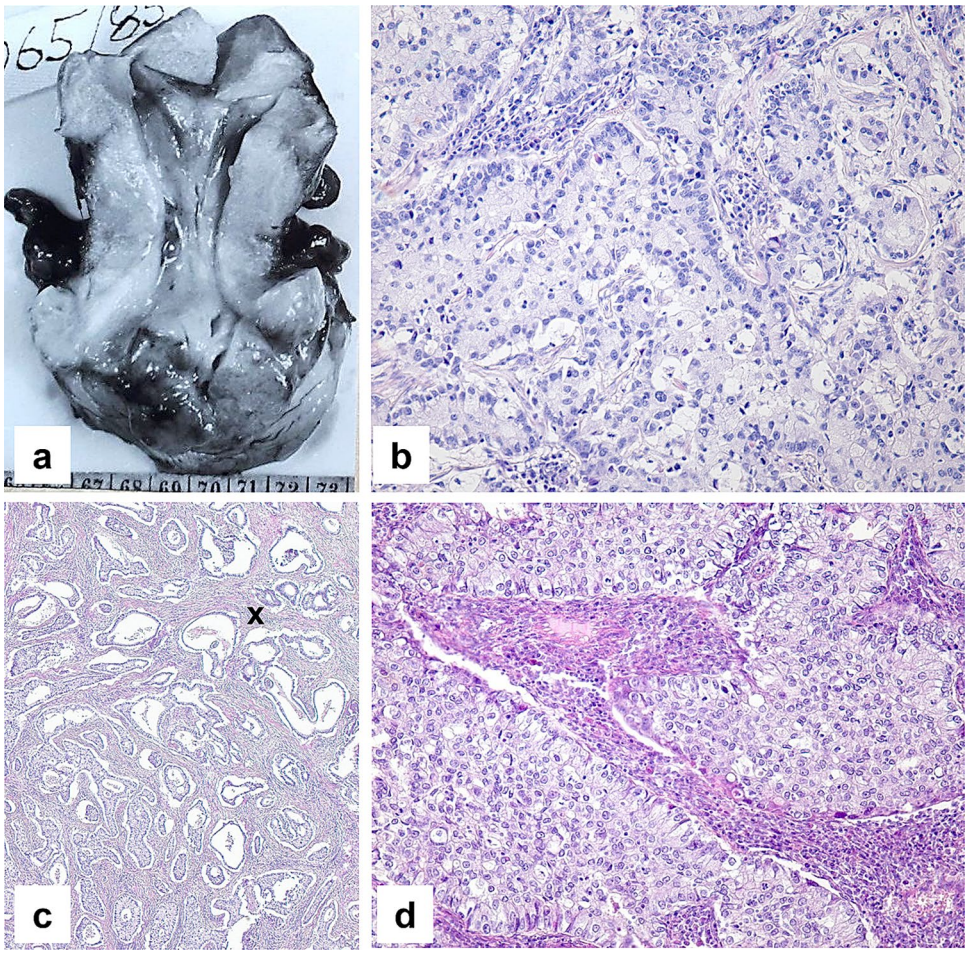


Fig. 2 Macroscopic and histologic appearance of pure i-SMILE and a case admixed with endocervical adenocarcinoma of the usual type. **a, b** Radical hysterectomy specimen with a small exophytic tumor confined to the uterine cervix (**a**) histologically representing mucinous adenocarcinoma with features of i-SMILE; **c, d** mixed tumor with glandular morphology (X), representing cervical adenocarcinoma of the usual type, mixed with i-SMILE, large magnification representing i-SMILE with strong peritumoral inflammatory response (**d**) and finger-like pattern of invasion

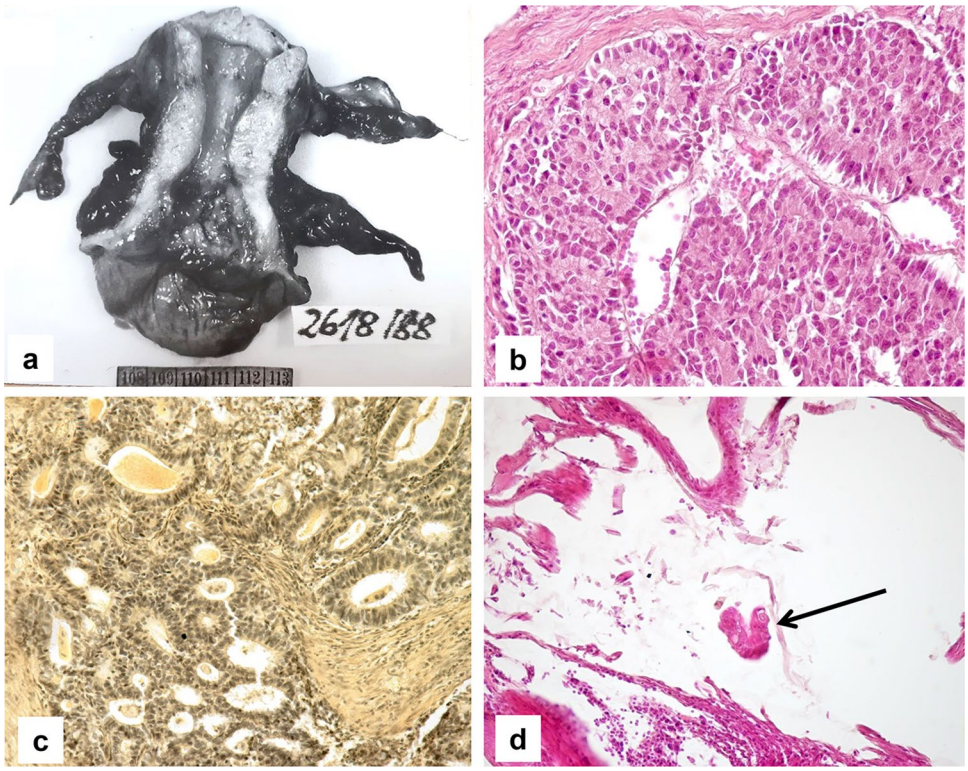
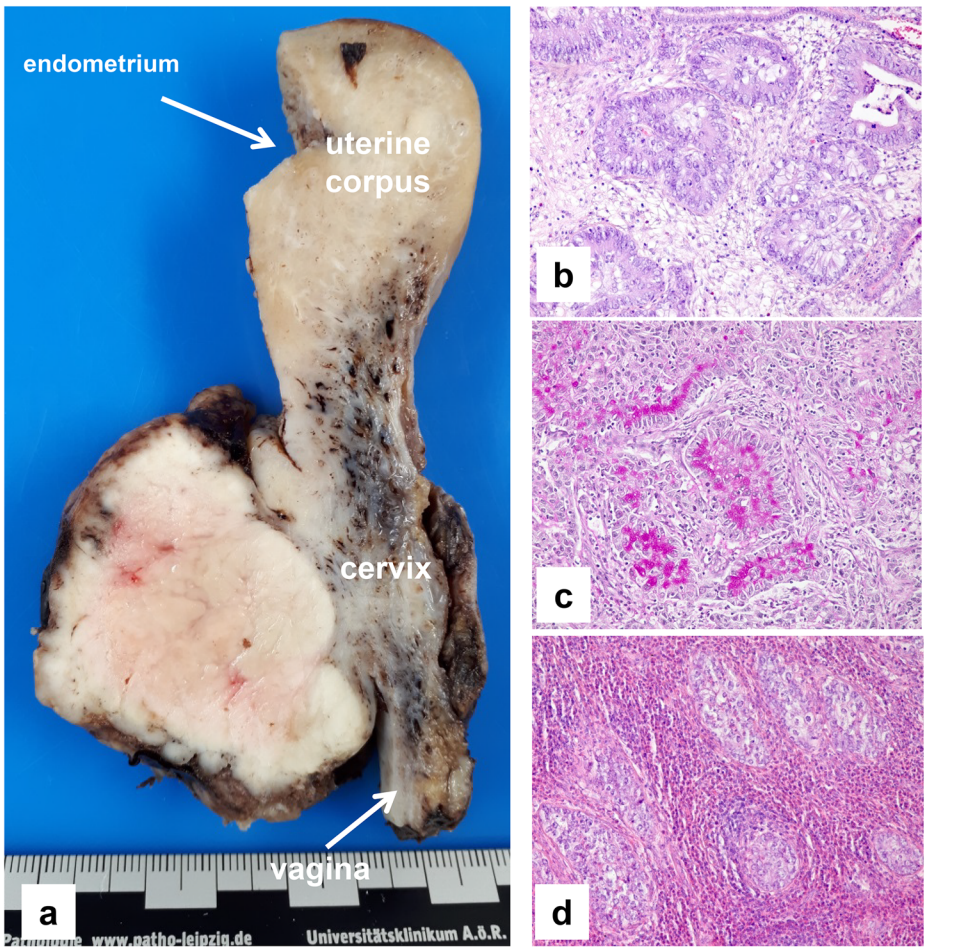
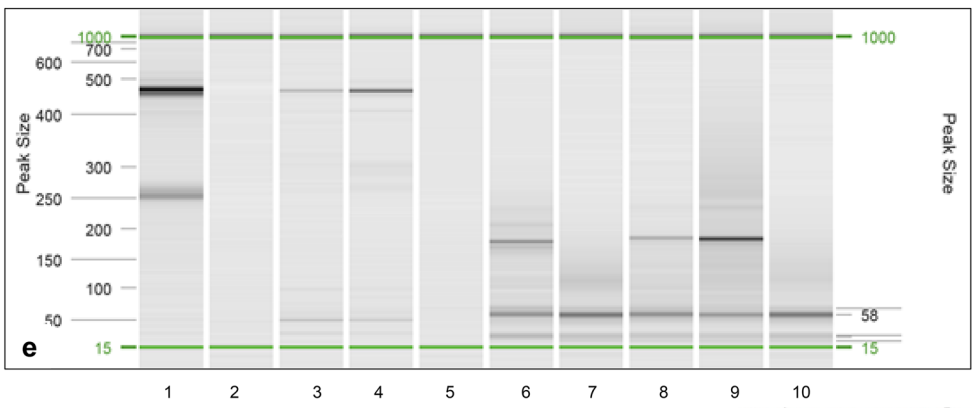
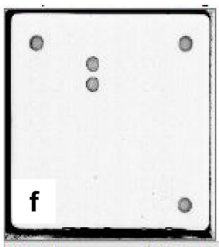


Fig. 3 Pathologic findings of an i-SMILE, histopathologically admixed with endocervical adenocarcinoma of the usual and mucinous type. **a** Radical hysterectomy representing a polypous-exophytic tumor protruding out of the cervical os; **b** poorly differentiated component of the tumor, representing features of i-SMILE, admixed with; **c** glandular growth pattern, representing cervical adenocarcinoma of the usual type and; **d** mucinous adenocarcinoma colloid type with small tumor cell nests (arrow) floating within mucinous material





1: positive control
2: negative control
3: 38746/17 40 ng DNA
4: 38746/17 200 ng DNA
5: extraction control 1-5: Primer mix My11/09 (expected size: ~450 bp)
6: positive control
7: negative control
8: 38746/17 40 ng DNA
9: 38746/17 200 ng DNA
10: extraction control 6-10: Primer mix 125 (expected size: ~125-155 bp)



Identity	Value
Hyb-Control	27985
Type 18	25494

Fig. 4 Pathological findings of pure i-SMILE and with the detection of HPV high-risk infection. **a** Sagittal cut of the hysterectomy specimen representing a large exophytic tumor; i-SMILE infiltrating cervicals wall with nest-like appearance (**b**) with intracytoplasmic positive staining for PAS (**c**), surrounded by dense peritumoral inflammatory response, mainly composed of eosinophils (**d**); **e, f** plot for the detection of high-risk HPV infection by type 18

The mean age of the patients at our hospital was 46.6 years (range 34–61 years) with a mean tumor size of 5.7 cm (4.1–6.4 cm). All tumors represented a polypous and exophytic growth (Figs. 1a, c, 2a, 3a, 4a).

A mean number of 39 pelvic lymph nodes (range 26–79) were removed. During a mean follow-up of 16.4 months (range 11–28 months), all patients had recurrence during a mean time of 8 months (range 6 weeks–12 months) and four out of five patients died of the disease, representing a mean overall survival time of 17.7 months (range 12.5–28 months). One patient is alive with the disease. Two patients represented distant metastatic spread (one within the lungs and one within the inguinal lymph nodes, the liver and the skin).

The histopathologic findings are illustrated in Figs. 1, 2, 3 and 4.

The detailed descriptions of the case histories, treatment approaches as well as the histopathological findings of the Leipzig cases are available at the supplementary material.

Histopathological, immunohistochemical and PCR analyses

Three cases represented with mixed histology of i-SMILE and different histologic subtypes of cervical adenocarcinomas (Figs. 2, 3).

All of our cases showed an infiltrative growth of tumor cell nests with a finger-like pattern of invasion (Figs. 1d, e, 2d, 4b, d), accompanied by a strong peritumoral inflammatory response with a predominance of neutrophils (Figs. 1e, g, 2d, 4d). Neutrophils were only seen in the invasive stratified mucin-producing carcinoma component (Figs. 1e, 2d) and were entirely absent in the invasive endocervical adenocarcinoma component cases with mixed histology (Figs. 2c, 3c).

The detection of HPV infection by PCR was informative in only two out of the five cases and represented a co-infection of HPV-type 18 and 39 in one and HPV 18 in the other case (Figs. 1, 4e, f). The other three cases were not informative because DNA extraction failed by fragmentation of the DNA done by inappropriate fixation. These cases dated back to the diagnostic years 1985, 1996 and 1988.

All tumors revealed strong and diffuse immunohistochemical staining with p16 (Fig. 1f).

Characteristics of the published cases

Several morphology-based studies have not given any detailed information about clinical presentation and treatment approaches (Park et al. 2013; Boyle and McCluggage 2015; Stolnicu et al. 2018) and were excluded from further evaluation.

Eight cases of i-SMILE with available clinical and prognostic data have been published previously (Lastra et al. 2016; Onishi et al. 2016). The majority of cases were diagnosed in FIGO stage IB1 (6/8), which occured in pre-menopausal women (6/8) and were treated by radical hysterectomy (6/8). There are no details within the reports about the number of resected pelvic lymph nodes. Follow-up information were available in six cases. Three out of five cases reported by Lastra et al. (2016) presented with pulmonary metastases or died of the disease. Surprisingly, all three patients in the report of Onishi et al. (2016) were alive without evidence of disease after a median of 59.3 months.

Clinicopathological and prognostic findings of the series from Leipzig University Hospital and cases obtained from the literature are summarized in Table 1.

Discussion

SMILE is a recently recognized distinct type of precursor lesion of invasive cervical adenocarcinoma (AC; Park et al. 2000; Lastra et al. 2016; Boyle and McCluggage 2015). In 2016, an invasive AC with features of SMILE was first described and termed stratified mucin-producing AC (ISMC or i-SMILE; Lastra et al. 2016; Onishi et al. 2016). On average, patients with pure SMILE were 15 years younger than those with i-SMILE (Lastra et al. 2016). This time interval is concordant with the presentation of (conventional) AIS 10–15 years earlier than invasive AC (Wilbur et al. 2014) and reflects a stepwise progression from the intraepithelial precursor (SMILE) to the invasive AC (i-SMILE). As shown in Table 1 and the data from the literature (Park et al. 2000; Onishi et al. 2016; Lastra et al. 2016), up to 75% of i-SMILE include concordant SMILE, but SMILE may be overgrown by the invasive tumor during disease progression.

HPV high-risk DNA can be detected in the majority of cervical adenocarcinomas (Loureiro and Oliva 2014). Some studies have shown that SMILE is also associated with high-risk HPV infections (Sano et al. 2014; Lastra et al. 2016) and concomitant strong as well as diffuse p16-expression (Lastra et al. 2016; Onishi et al. 2016; Boyle and McCluggage 2015), which is also present in i-SMILE (Onishi et al. 2016; Stolnicu et al. 2018). The analysis of our cases demonstrated high-risk HPV in all of the informative cases and p16-overexpression in all tumors (Fig. 1f) supporting the hypothesis that high-risk HPV is associated with tumor development. As reported for other histologic subtypes of cervical AC (Park et al. 2013), the majority of i-SMILE are also associated with HPV-type 18.

The mean age of the reported cases with i-SMILE is 47.1 years (range 34–66 years; Table 1), which is similar to invasive squamous cell and other histologic subtypes of

Table 1 Summary of the clinicopathologic data, treatment and follow-up information of patients with invasive SMILE

No.	Age (years)	Symptoms lesion	Precursor size	Tumor	Histology	Stage	Treatment	Follow-up
Lastra et al. (2016)								
1	64	NA	SMILE, H-SIL, AIS	1.7 cm	i-SMILE	FIGO IB1	Radical hx	Pulmonary mts (36 months)
2	44	Vag. bleeding, cervical mass	SMILE	1.2 cm	i-SMILE	FIGO IB1	NA	NA
3	39	PAP + ve, cervical mass	NA	6.0 cm	i-SMILE	FIGO IIB inguinal LNM	RCX	Pulmonary mts (9 months)
4	38	Vag. bleeding, cervical mass	SMILE	2.5 cm i-SMILE	FIGO IB1	Radical hx	NA	
5	45	PAP + ve, ascites	SMILE	1.9 cm	i-SMILE	FIGO IB1	Radical hx bilateral adnexal mts, perito-neal mts	DOD (1.5 months) palliative care
Onishi et al. (2016)								
6	40	Vag. bleeding	SMILE, AIS	2.5 cm	i-SMILE, SCC	FIGO IB1	Radical hx, CX	Alive (126 months)
7	44	Vag. bleeding	SMILE, H-SIL	5.0 cm	i-SMILE	FIGO IIB,p N1	Radical hx, RX	Alive (39 months)
8	66	Vag. bleeding	SMILE, AIS	3.0 cm	i-SMILE	FIGO IB1	Radical hx	Alive (13 months)
Present study (please see Figs. 1–4)								
9	59	Cervical mass bleeding after sexual intercourse	SMILE	6.4 cm	i-SMILE	pT1b2 pN1	TMMR, t-LNE, CX	Pelvic recurrence (10 months), treated with LEER inguinal cutaneous MTS treated with topotecan and RX DOD (4 months)
10	38	Atypical Pap smear, cervical mass	NA[1)]	5.5 cm	i-SMILE + NOS	pT2a2 pN1	Radical hx, radical pelvic LNE, RX	Pelvic recurrence (12 months), DOD (28 months)
11	34	Vaginal discharge	NA[1)]	6.0 cm	i-SMILE + NOS	pT2b pN1	Radical hx, radical pelvic LNE, RX	Pelvic recurrence (9 months), treated with LEER & CORT DOD (4.5 months)
12	61	Post-menopausal bleeding, cervical mass	NA[1)]	4.1 cm	i-SMIL + endo-	pT1b1 pN1 metrioid + colloid-mucinous AC	Radical hx, radical pelvic LNE, RX	Vaginal and pelvic recurrence (9 months), DOD (3.5 months)
13	41	Vag. bleeding, pelvic discomfort, bleeding after sexual intercourse	SMILE	6.4 cm	i-SMILE	pT2b pN1	TMMR t-LNE, CX	Pelvic recurrence (6 weeks), cM1 PUL, LYM treated with CX + bevacizumab, no residual pulmonary disease on CT-scan but 2.3 cm pelvic side wall recurrency (10 months) treated with CX

AIS adenocarcinoma in situ, *cM1* clinically distant metastatic disease, *CORT* combined operative and radiotherapeutic treatment, *CX* chemotherapy, *DOD* dead of disease, *H-SIL* high-grade squamous intraepithelial lesion, *Hx* hysterectomy, *i-SMILE* invasive stratified mucin-producing carcinoma, *LEER* lateral extended endopelvine resection, *LNM* lymph node metastases, *LYM* lymph nodes, *Mts* metastases, *NA* not applicable, *NA[1)]* precursor lesion(s) may be overgrown by the invasive tumor, *NOS* endocervical adenocarcinoma usual type (syn. not otherwise specified), *PUL* pulmonary, *RCX* chemo-radiation, *SCC* squamous cell carcinoma, *SMILE* stratified mucinous intraepithelial lesion, *t-LNE* therapeutic lymph node resection, *TMMR* total mesometrial resection,

invasive adenocarcinomas of the uterine cervix (Stolnicu et al. 2018).

Overall, the majority of i-SMILEs show a pure stratified mucin-producing histology (9/13; 69.2%). Mixed cases were reported to be accompanied by adenocarcinoma of the usual, endometrioid or colloidal type (Figs. 2, 3) or squamous cell carcinoma (Onishi et al. 2016; Lastra et al. 2016). Neuroendocrine carcinomas which may be associated with other types of cervical ACs and rarely associated with a very poor prognosis (Ganesan et al. 2016; Horn et al. 2006) have not yet been reported to be associated with i-SMILE. The reports of Park et al. (2000) and Boyle and McCluggage (2015) describe an association of the intraepithelial SMILE with an invasive carcinoma (adeno-, squamous cell or adenosquamous) in 10–60%. However, both studies did not report i-SMILE in their cases.

There is a wide range of tumor size with a mean size of 4.0 cm (range 1.2–6.4 cm; Table 1), and the majority of cases were diagnosed with tumors > 2 cm (9/13; 76.9%). Typically (7/8; 87.5%), i-SMILE shows a polypoid and exophytic appearance (Fig. 1a, 2a, 3a, 4a).

Regardless of the histologic subtype, the presence of pelvic/para-aortal lymph node metastases, local extension of the disease (tumor stage) as well as tumor size (Takeda et al. 2002; Singh and Arif 2004) are well-established prognostic factors of cervical carcinomas. The same parameters have been reported to be of prognostic impact for cervical ACs (Baalbergen et al. 2004). More recently, it was shown that HPV-negative cervical AC may be associated with a poor prognosis (Rodríguez-Carunchio et al. 2015; Singh and Gilks 2017). Although not extensively studied, the available data for gastric-type cervical AC suggest an aggressive behavior and a worse prognosis, including a possible propensity for early peritoneal and abdominal dissemination (Karamurzin et al. 2015; Kojima et al. 2007; McCluggage 2013; Talia and McCluggage 2018). Kojima et al. (2007) reported a 5-year disease-free survival of 30% for the gastric-type compared to 74% for usual endocervical-type AC. Additionally, cervical AC with a minimal deviation-type growth pattern (MDA) may be associated with a poor prognostic outcome (Gilks et al. 1989; Li et al. 2010). Regardless of tumor stage, the presence of pelvic lymph node involvement and the histological tumor type, patients treated with TMMR showed an excellent prognosis. At a median follow-up of 41 months, the 5-year disease-free and overall survival probabilities were 94% [95% CI 90–98%] and 96% [95% CI 93–99%], and for those with positive nodes 81% [95% CI 67–94%] and 91% [95% CI 81–100%], respectively (Höckel et al. 2009).

The two patients of our study who underwent the TMMR approach for tumor resection developed a central pelvic recurrence after 10 months and 6 weeks, respectively. Two of the five patients with i-SMILE reported by Lastra et al. (2016) showed parametrial involvement and histologically proven pulmonary metastases within 9 and 36 months during follow-up. One patient presented with widespread peritoneal disease at the time of diagnosis and died 1.5 months later. Surprisingly, all patients in the report of Onishi et al. (2016), including one with parametrial extension, were alive during a mean follow-up of 59.3 months (Table 1). Summarizing the data from Table 1, 7 out of the 11 informative patients (63.3%) developed recurrent disease after a mean of 12.2 months (range 6 weeks–36 months). Four patients developed distant metastases (3 × lungs, 1 × inguinal lymph nodes, 1 × cutaneous).

There is a heterogeneous treatment approach for patients with i-SMILE, provided in the published reports. One of our patients with a central pelvic recurrence responded well to a combined chemotherapy with cisplatin, paclitaxel and bevacizumab (see case 4 in the supplementary material).

The present data and those obtained from the literature suggest that i-SMILE represent a distinct subtype of invasive endocervical adenocarcinoma, associated with SMILE as its precursor lesion and high-risk HPV-infection, mainly with HPV type 18. The majority of cases are associated with a large tumor size and pelvic lymph node involvement at the time of diagnosis. Regardless of the tumor size and the local tumor stage, i-SMILE may represent an aggressive tumor with early recurrent disease and a substantial risk of distant metastatic disease.

Funding The authors declare that there was no funding for the study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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