Journal of Gynecology Obstetrics and Human Reproduction 48 (2019) 319–327

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Original Article

Clinicopathological characteristics of patients with mucinous adenocarcinoma of the uterine cervix: A retrospective study of 21 cases

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ARTICLE INFO

Article history:
Received 26 November 2018
Received in revised form 28 January 2019
Accepted 19 February 2019
Available online 23 February 2019

Keywords:
Mucinous adenocarcinoma
Gastric type
Intestinal type
Malignant adenoma
Signet-ring cells
Uterine cervix

ABSTRACT

Objectives: Few studies in the literature take into account the WHO's 2014 redefinition of the characteristics of mucinous adenocarcinoma of the uterine cervix. Our objective was to describe the characteristics of a group of these patients.
Material and methods: This was a retrospective descriptive study of patients diagnosed between 1 January 2005 and 31 May 2016 in three hospitals in Lyon, France. All the cases of cervical adenocarcinoma were reanalysed by an expert in gynaecological pathology to retain the mucinous subtypes as defined in the 2014 WHO classification. We analysed their clinical and pathological characteristics.
Results: Among the 82 cases of cervical adenocarcinoma, 21 (26%) were diagnosed as mucinous. Ten were gastric type, of which four were in the extremely well differentiated form of minimal deviation adenocarcinomas, six were intestinal type, two were signet-ring cell type, and three were not otherwise specified. The patients' mean age was 42 years and 18 patients were premenopausal. The revealing symptom was metrorrhagia in eight cases (38%) and mucinous vaginal discharge in four (19%). Fifteen (72%) of the cervical smear were abnormal. Five (31%) of the 16 patients with gastric or intestinal type adenocarcinoma had a specific radiological presentation: multiple cysts of the uterine isthmus, visible on ultrasound and with T2 hyperintensity on MRI.
Conclusion: Mucinous adenocarcinoma is a rare form of cervical cancer that can be confused with other pathological types. It can be detected using cervical smears and should be suspected in cases of mucinous discharge and characteristic MRI features.

Introduction

Adenocarcinoma of the uterine cervix accounts for 20–25% of all cervical cancers [1,2]. Its incidence has increased over the past decades while that of squamous cell carcinoma has decreased thanks to the screening procedures established in developed countries [2,3]. It affects women at a younger age than squamous cell carcinoma does [4]. Around 90% of all cervical adenocarcinomas are of the classic endocervical type [5]. Mucinous adenocarcinomas of the cervix are a subgroup redefined in the 2014 WHO classification (Appendix A) [5]. They are rare, poorly studied from a clinical point of view in the literature and, to our knowledge, have never been analysed as a subtype since the WHO updated its classification.

Mucinous adenocarcinomas of the uterine cervix are an important diagnostic and therapeutic issue for pathologists, radiologists and gynaecologists. They appear to have specific characteristics that need to be studied. The increase in their relative incidence warrants the development of effective diagnostic and treatment measures. The objective of this study was therefore to gather and describe a series of cases of mucinous adenocarcinoma of uterine cervix.

Material and methods

This was a retrospective descriptive study of all recorded cases of cervical adenocarcinoma between 1 January 2005 and 31 May 2016 at three hospitals in Lyon, France (Hôtel-Dieu, Croix-Rousse, and Lyon-Sud).

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http://dx.doi.org/10.1016/j.jogoh.2019.02.002
2468-7847/

All the adenocarcinoma slides were reinterpreted by a specialist in gynaecological tumour pathology (MD), and then classified using the 2014 WHO criteria [5]. The inclusion criterion was the presence on the slides of a gastric, intestinal or signet-ring cell type adenocarcinoma of the mucinous subtype. Adenocarcinomas that were poorly differentiated or of an indeterminate morphology were classed as not otherwise specified (NOS). All other subtypes of adenocarcinoma were excluded.

A number of cases were referrals from other medical centres. We contacted the corresponding pathology laboratories to identify the referring surgeon. We then obtained the patients' medical records from their gynaecologists and anonymized the data. We also analysed the patients' records in the study centres' archives. The patients' characteristics were gathered in an Excel file. The patient characteristics recorded were: age at diagnosis, smoking habit, hormonal risk factors (menopausal status, use of contraception, gravidity, parity), presence of a known genetic condition, previous cervical smears, revealing symptoms (spontaneous or induced metrorrhagia, vaginal discharge, pelvic pain), clinical examination results at diagnosis, pretherapeutic cytology and/or histology, paraclinical tests (tumour markers, ultrasound imaging, CT, MRI, PET scan), tumour size and FIGO stage according to the 2009 classification (Appendix B), treatment (surgery, radiotherapy, chemotherapy, brachytherapy), histological and immunohistochemical results, evolution after treatment (complications, survival, recurrence) and follow-up time after diagnosis. The adenocarcinoma subtype was diagnosed morphologically; we did not repeat the immunohistochemical analysis for this study. The data interpreted in this study were therefore obtained at the time of diagnosis. The cancer stage was considered early for FIGO stages IA, IB and IIA, and advanced for stages IIB, III and IV.

Results

A total of 89 cases recorded as cervical adenocarcinoma were analysed. Seven were excluded on review: six were endometrial adenocarcinomas and one was a rectal adenocarcinoma that had invaded the cervix. Twenty-two of the remaining 82 cases were

Table 1
Clinical characteristics of the patients and tumours by histological subtype.

Type	Gastric[a] ($n=10$)	Intestinal ($n=6$)	Signet-ring cell ($n=2$)	Not otherwise specified ($n=3$)	Total n (%)
FIGO stage					
I	6	6	1	2	15 (71)
IA	0	2	0	1	
IB	6	4	1	1	
II	3	0	1	1	5 (24)
IIA	2	0	0	0	
IIB	1	0	1	1	
III	0	0	0	0	0 (0)
IIIA	0	0	0	0	
IIIB	0	0	0	0	
IV	1	0	0	0	1 (5)
IVA	0	0	0	0	
IVB	1	0	0	0	
Stage[b]					
Early	8	6	1	2	17 (81)
Advanced	2	0	1	1	4 (19)
Age at diagnosis (years)					
< 30	0	1	1	1	3 (14)
30–49	6	5	1	1	13 (62)
≥ 50	4	0	0	1	5 (24)
Parity[c] ($n=19$)					
0	2	1	0	2	5 (26)
1 or 2	6	1	0	1	8 (42)
≥ 3	2	2	2	0	6 (32)
Premenopausal	9	5	2	2	18 (86)
Symptoms[d]					
None	1	5	0	2	6 (29)
Pelvic pain[e]	5	0	1	1	7 (33)
Metrorrhagia	4	1	2	1	8 (38)
Mucinous discharge	3	0	1	0	4 (19)
Contraception[c]					
None	3	2	0	1	6 (29)
Intrauterine device	3	0	0	0	3 (14)
Copper	2	0	0	0	2 (9)
Hormonal	1	0	0	0	1 (5)
Progestin implant	0	1	0	0	1 (5)
Combined pill	0	0	0	1	1 (5)
Smoking status[c]					
Never smoked	4	0	1	1	6 (29)
Active	1	1	0	1	3 (14)
Quitter	3	0	0	0	3 (14)
HPV[c]					
Positive[f]	1	3	1	1	6 (29)
Negative	1	0	0	1	2 (9)

[a] Includes minimal deviation mucinous adenocarcinomas.
[b] FIGO tumour stages IA, IB and IIA were classed as early, stages IIB, III and IV as advanced.
[c] Data missing for some patients.
[d] Some patients had several symptoms.
[e] Spontaneous pelvic pain, dyspareunia and/or pelvic fullness.
[f] HPV 16 and 18.

identified as being mucinous adenocarcinomas by reinterpreting the histological slides. Five of these concerned patients treated in one of the three study centres and 17 were referrals. One of the latter was excluded after reanalysis of the surgical specimen revealed that it was in fact an endometrial adenocarcinoma.

The final dataset consisted of 21 cases of mucinous adenocarcinoma of the uterine cervix. Their pathological characteristics were as follows: 10 (48%) were gastric (G) type adenocarcinomas, of which four were minimal deviation (MD, i.e. extremely well differentiated) adenocarcinomas, six (29%) were intestinal (I) type, two (10%) were signet-ring cell (SRC) type, and three (14%) were NOS. The cervical samples used for the histological diagnosis were in 10 cases biopsies (for four non-MD G-type, one MDG-type, one I-type, two SRC-type and two NOS adenocarcinomas), nine conization specimens (two non-MD G-type, two MDG-type and four I-type adenocarcinomas), and two hysterectomy specimens (one MDG-type and one NOS adenocarcinoma).

Clinical characteristics

The clinical characteristics of the patients are shown in Table 1. The mean age of the patients at diagnosis was 42 years (range, 20–74 years) overall. In terms of the subgroups, the mean age was 46 years (33–74 years) for the patients with a G-type adenocarcinoma (specifically 52 years (33–74 years) for those with MDG-type and 42 years (34–50 years) for those with other G-type adenocarcinomas); 39 years (29–46 years) for those with an I-type adenocarcinoma, 36 years (29 and 42 years) for the two patients

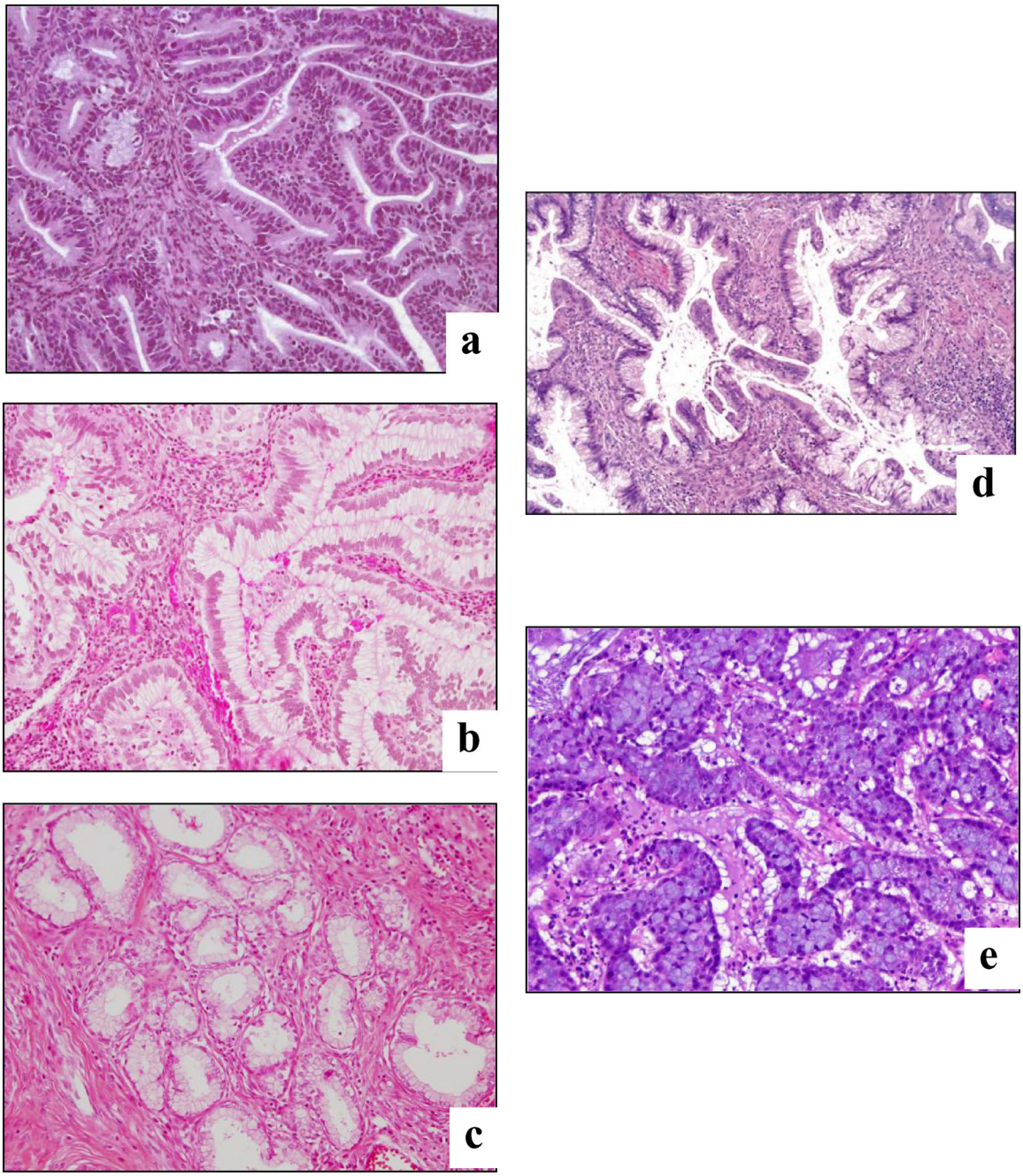

Fig. 1. Histological aspect of various forms of mucinous cervical adenocarcinomas: (a) classic, (b) gastric type (not extremely well-differentiated), (c) gastric type minimal deviation, (d) intestinal type and (e) signet-ring cell type.

with an SRC-type adenocarcinoma, and 38 years (20–60 years) for those with a NOS mucinous adenocarcinoma.

The mean size of the tumours was 29.3 mm (4–80 mm) and was measured histologically in 13 cases and radiologically (by MRI) in 8 cases. The latter were only available when the patients received neoadjuvant concomitant radiochemotherapy or when tumour size was not included in the original pathological analysis. Four patients (three with a G-type including one with an MDG-type and one with a NOS mucinous adenocarcinoma) had peritoneal carcinomatosis either initially or during follow-up.

The most frequent symptoms were metrorrhagia, spontaneous or induced, followed by pelvic pain, spontaneous or induced (dyspareunia). Two of the patients with a G-type adenocarcinoma (one, a MDG-type) had a history of borderline mucinous ovarian cysts.

On colposcopy, the cervix was clinically healthy in seven patients. Two patients had moderate anomalies, one had signs of cervicitis, one had a polyp projecting from the cervix and cervicitis, four had an enlarged and/or hardened cervix, and five had a voluminous mass. Details of the clinical aspect of the cervix were missing for one patient.

Cytological and histological characteristics

The cytological, histological and immunohistochemical characteristics of the adenocarcinomas are illustrated in Figs. 1 and 2

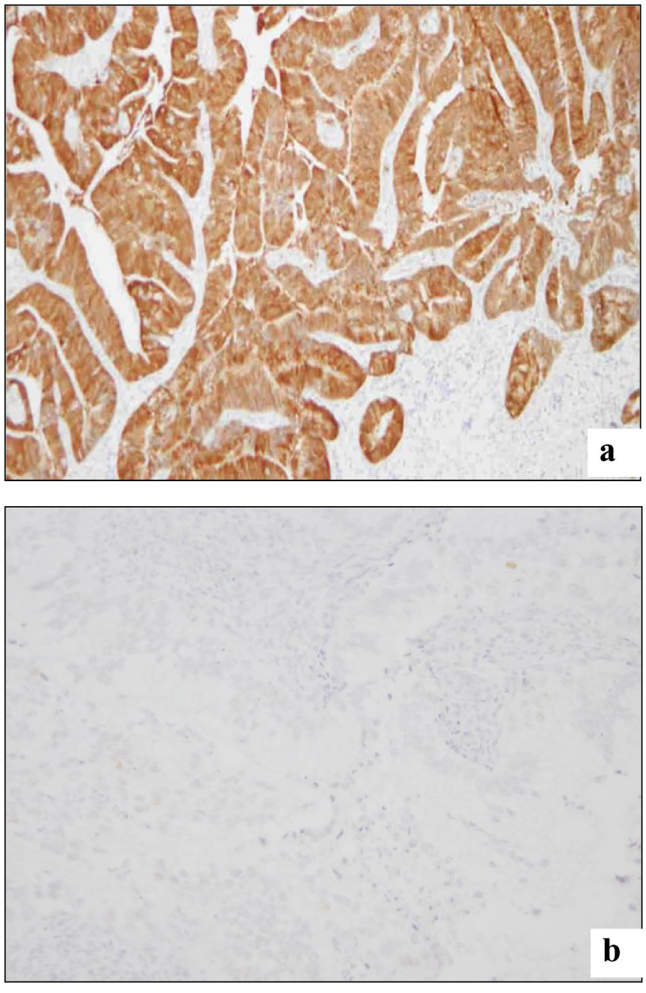

Fig. 2. Histological aspects of (a) a classic cervical adenocarcinoma with positive p16 immunostaining and (b) a gastric-type mucinous cervical adenocarcinoma with negative p16 staining.

and Tables 2 and 3. Biopsies had allowed the diagnosis to be reached preoperatively for 4/10 patients with a G-type adenocarcinoma (including one out of four of those with a MD adenocarcinoma), one out of six of those with an I-type and both of those with a SRC-type adenocarcinoma. Thirty-nine percent of these 18 biopsies were therefore contributive.

The non-MD G-type adenocarcinomas (Fig. 1b) presented as an adenocarcinomic tumoural proliferation of variable sized irregular glandular structures, some with a papillary aspect, infiltrating the cervical stroma in a disordered manner. There were fibrous or oedemous, in some cases inflammatory, desmoplastic stromal reactions containing small, irregular, angular-sided glands. The glandular structures were lined by an unstratified high cylindrical epithelium, with very abundant gastric mucus secretion, with an eosinophilic aspect. The cells were cylindrical with an eccentric nucleus, sometimes with nuclear atypia, at the basal pole. Lobular endocervical glandular hyperplasia was observed for one patient.

The MDG-type adenocarcinomas (Fig. 1c) presented as a proliferation of variable sized, irregular glands, lined with a pyloric-type mucus-secreting unstratified cylindrical epithelium with a clear cytoplasm, pushing the nucleus to the base. The nuclei were rounded, uneven and vesicular, with rare mitosis. Some of the glands were cystic and sometimes broken, with a macrophagic reaction to contact. This was associated with desmoplastic stroma reaction.

The I-type adenocarcinomas (Fig. 1d) presented a cribriform structure with a fibrous stroma reaction around atypical glands. The lining was stratified and cylindrical and surrounded goblet cells and intestinal-type mucous secretions. There were cytonuclear atypia, mitoses and areas of mucous retention.

The aspect of the SRC-type adenocarcinomas (Fig. 1e) was a high-grade carcinomatous proliferation with tumour masses composed of highly mucus-secreting cells and intracytoplasmic mucus that pushed the nuclei to the periphery, giving a signet-ring aspect.

The data from the patient files did not contain immunohistochemical data. At the time of diagnosis indeed, immunohistochemical analyses for MUC6 and HIK1083 were not routinely carried out.

In 14 (67%) of the 21 cases, the initial pathological assessment was incorrect and the diagnoses of a mucinous adenocarcinoma and its subtype were only made after reinterpretation by the expert pathologist. In 6 of these 14 cases, endocervical adenocarcinoma was correctly diagnosed but no subtype was specified. Four of the non-MD G-type, one of the I-type and one of the SRC-type adenocarcinomas were described simply as “mucinous adenocarcinoma”. The two others were wrongly classified one as a glassy-cell carcinoma instead of as an SRC-type adenocarcinoma and the other as a villoglandular carcinoma rather than as a NOS mucinous adenocarcinoma.

Radiographic characteristics

Imaging data were available for 14 patients. Among the six patients with a non-MD G-type adenocarcinoma, two had a visible tumour or cervical mass, one had an enlarged cervix, and one patient had multiple cysts in the cervical isthmus, with no identifiable mass. The only available ultrasound data was for one of the four patients with an MDG-type adenocarcinoma. This showed an echogenic nodule in the isthmus, with a scattering of cystic structures.

The MRI reports for five of the patients with a non-MD G-type adenocarcinoma described lesions with T2 hyperintensity and enhancement after gadolinium injection. For the patients with a MDG-type adenocarcinoma and MRI data, these showed sometimes microcystic nodular masses with T2 hyperintensity and T1

Table 2
Cytological and histological characteristics of the patients and tumours by histological subtype.

Type	Gastric[a] ($n=10$)	Intestinal ($n=6$)	Signet-ring cell ($n=2$)	Not otherwise specified ($n=3$)	Total n (%)
Cytology ($n=18$)					
NILM	3[b]	1[b]	0	1[b]	**5 (28)**
Abnormal	6[b]	4[b]	2	1[b]	**13(72)**
LSIL	2	0	0	0	2
HSIL	0	1	0	0	1
ASC-US	0	0	1	0	1
AGC	3	3	1	1	8
ASC-H	1	0	0	0	1
Tumour size (mm)					
< 40	6	5	1	2	14 (67)
≥ 40	4	1	1	1	7 (33)
Lymph node invasion	3	1	2	0	6 (29)
Metastasis	2[c]	0	0	0	2 (9)
Ovarian invasion	3	1	0	0	4 (19)

AGC, atypical glandular cells; ASC-H, atypical squamous cells cannot rule out high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.
[a] Includes minimal deviation mucinous adenocarcinomas.
[b] Data missing for one patient.
[c] Occurred during follow-up for one patient.

Table 3
Immunohistochemical characteristics of the patients by histological tumour subtype.

Type	Gastric[a] ($n=10$)			Intestinal ($n=6$)			Signet-ring cell ($n=2$)			Not otherwise specified ($n=3$)		
	0	+	+++	0	+	+++	0	+	+++	0	+	+++
CEA	3[b]	2[b]	3[b]	0[b]	1[b]	1[b]	0[b]	0[b]	1[b]	1[b]	0[b]	1[b]
p16	7[b]	0[b]	2[b]	0[b]	0[b]	5[b]	0[b]	0[b]	1[b]	1	0	2
p53	3[b]	1[b]	0[b]	1[b]	0[b]	0[b]	1[b]	0[b]	0[b]	1[b]	0[b]	1[b]
ER/PR	8[b]	0[b]	0[b]	1[b]	0[b]	0[b]	1[b]	0[b]	0[b]	3	0	0
CK7	0[b]	0[b]	5[b]	0[b]	0[b]	2[b]	0[b]	0[b]	1[b]	0[b]	0[b]	2[b]
CK20	2[b]	1[b]	1[b]	1[b]	1[b]	0[b]	0[b]	0[b]	0[b]	1[b]	0[b]	0[b]

CEA, Carcinoembryonic Antigen; CK, cytokeratin; ER, oestrogen receptor; p16, cyclin-dependent kinase inhibitor 2 A; p53, tumour protein p53; PR, progesterone receptor; 0, no staining; +, focal staining; +++, diffuse staining.
[a] Includes minimal deviation mucinous adenocarcinomas.
[b] Data missing for some patients.

isointensity and enhancement after gadolinium injection (Fig. 3). Three MRI reports were available for patients with an I-type adenocarcinoma, two of which had visible lesions described as microcystic with T2 hyperintensity. The MR images for the two patients with SRC-type adenocarcinomas showed cervical lesions of intermediate intensity, measuring 38–40 mm along the long axis. One of these patients had a PET-scan, which confirmed the primitive nature of the cervical lesion. No MRI reports were available for the patients with NOS mucinous adenocarcinomas.

Treatment and evolution

The treatment regimens as a function of the FIGO stage are described in Table 4. Among the eight patients who only received surgery, six had a pelvic lymphadenectomy and one a lomboaortic lymphadenectomy. Among the nine patients who received surgery and radiotherapy (external or brachytherapy), one had a pelvic sentinel lymph node biopsy, eight a pelvic lymphadenectomy and three a lomboaortic lymphadenectomy.

The patients with G-type adenocarcinomas who had chemotherapy were treated using the following protocols: the one with a non-MD adenocarcinoma, FOLFOX; the one with a MD adenocarcinoma, radiochemotherapy with cisplatin and fluorourcail, followed by FOLFOX 4 (oxaliplatin + LV5FU2), as used to treat gastric tumours.

The mean follow-up time was 30 months (2–107 months). Five patients had tumour progression during treatment or had a recurrence. One patient with a SRC adenocarcinoma had a pelvic and lomboaortic lymph node recurrence 7 years after the initial treatment. One patient with a NOS mucinous adenocarcinoma had a recurrence with progression one month after treatment (surgery followed by adjuvant radiochemotherapy and brachytherapy). This progression was chemoresistant. One patient with a SRC and one with a non-MD G-type adenocarcinoma had progression under radiochemotherapy and brachytherapy. At the time the data for this study were gathered, 13 patients (62% of the study group) were alive and cancer-free, one was alive with the disease, three (14%) had died of the disease, one had died of another cause and three had been lost to follow-up after 3, 21 and 22 months respectively.

Discussion

Mucinous adenocarcinoma of the uterine cervix is a rare subtype of cervical cancer. We recorded about twenty cases in a decade in a referral centre for these pathologies. Identifying their clinical and histological characteristics is of interest nonetheless since the relative incidence of adenocarcinomas is increasing. Just over half (11/21) of the patients in our study group were symptomatic (metrorrhagia, pelvic pain, mucinous discharge). These signs should alert clinicians, particularly in case of abnormal cervical smears in young patients. Screening for these rare cancers is unfeasible because virology is only sensitive to HPV-induced adenocarcinomas and, although cervical smears were informative for some HPV-negative mucinous forms in our study, cytology is generally poorly sensitive in adenocarcinomas of the cervix [6]. Ultrasound imaging seems to be a good, accessible tool for diagnosis, complemented by MRI to characterise the lesion and assess locoregional extension. The diagnostic process should include biopsies if the cervix is clinically abnormal, with an MRI scan to explore extension. If the cervix is normal in a symptomatic patient, diagnosis requires a complete exploration of the uterus, including, imaging (ultrasound, MRI), and, if necessary, conisation and endocervical curettage to avoid missing lesions that are sometimes situated high in the endocervix, Finally, studying the immunohistochemical characteristics of these tumours appears crucial to help pathologists identify them based on specific immune markers.

The main strength of our study is that it is one of the first cases series of mucinous adenocarcinomas since the new WHO classification was published in 2014. This allows them to be characterised and to provide an overall clinical, histological and radiographic description. Our work outlines their general

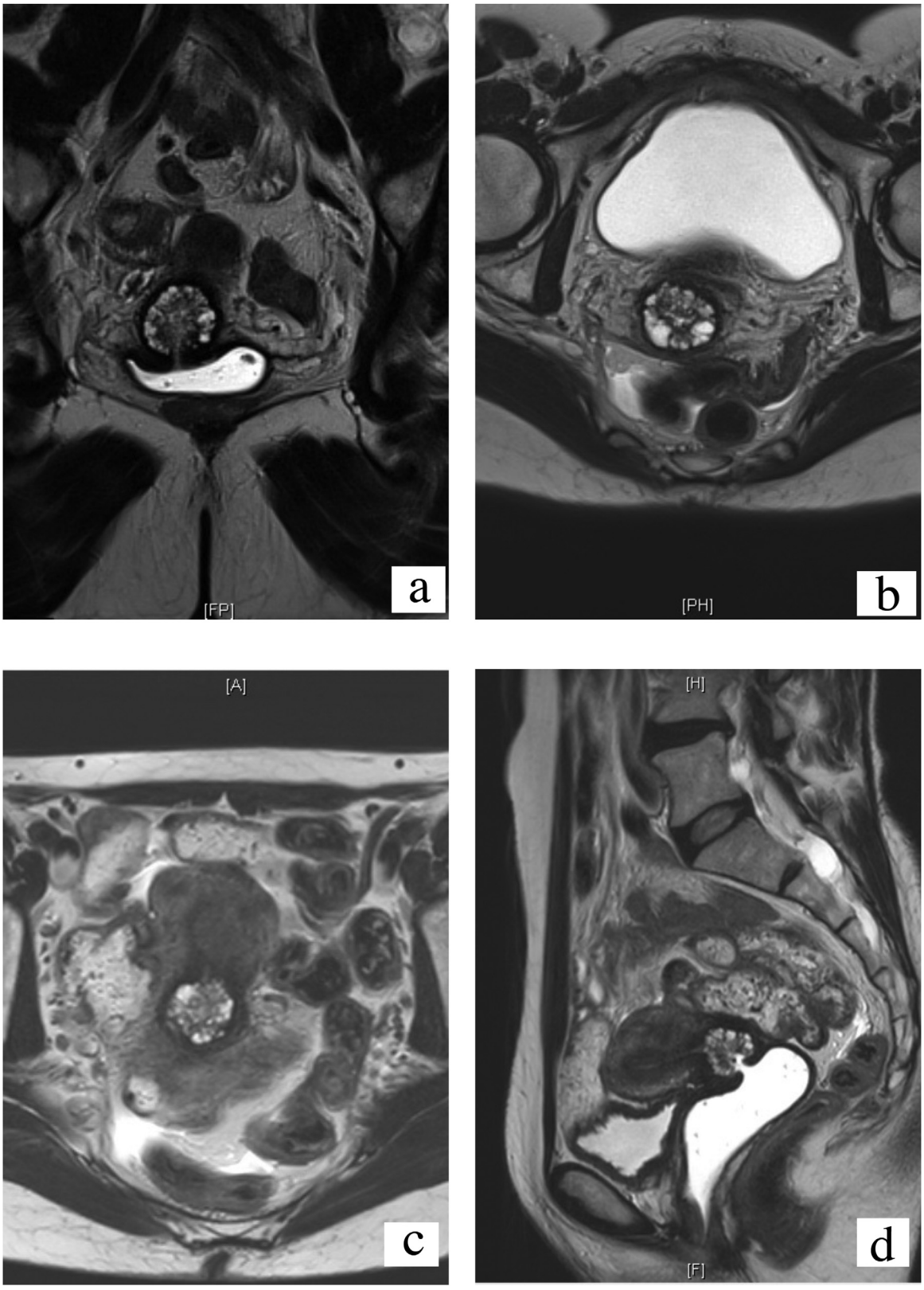

Fig. 3. Magnetic resonance images of a minimal deviation gastric-type adenocarcinoma of the cervix: (a) coronal T2-weighted, (b, c) axial T2-weighted and (d) turbo spin-echo sagittal T2-weighted.
Glossary: G-type, gastric type; I-type, intestinal type; MD, minimal deviation; SRC-type, signet-ring cell type.

Table 4
Treatment modalities for the 21 patients with mucinous cervical adenocarcinomas in terms of their FIGO stage.

FIGO stage	IA ($n=3$)	IB ($n=12$)	IIA ($n=2$)	IIB ($n=3$)	IV ($n=1$)	Total n (%)
Surgery alone	**2**	**6**	**0**	**0**	**0**	**8 (38)**
Conisation	1	1	0	0	0	2 (9)
Extrafascial hysterectomy	1	1	0	0	0	2 (9)
Enlarged colpohysterectomy	0	4	0	0	0	4 (19)
Surgery and radiotherapy[a]	**1**	**2+2**[b]	**2**[b]	**1+1**[b]	**0**	**9 (43)**
Extrafascial hysterectomy	0		1		0	3 (14)
Enlarged colpohysterectomy	1	0	1	2	0	6 (29)
		4		0		
Radiotherapy alone	**0**	**2**[b]	**0**	**1**	**0**	**3 (14)**
Palliative treatment	**0**	**0**	**0**	**0**	**1**	**1 (5)**

[a] External radiotherapy and brachytherapy.
[b] These patients also received concomitant chemotherapy.

characteristics and promotes a greater focus on these little known forms of cervical cancer. The weaknesses of the study are its retrospective nature and the absence of any immunohistochemical analysis. This is because specific markers have only recently been described and were not routinely investigated at the time the patients in this study were diagnosed.

Since mucinous adenocarcinomas have only recently been included as a subtype [5], their distribution among the different forms of adenocarcinomas has not yet been described in the literature. They are overrepresented in our study because of recruitment bias, many of the cases being referrals to a pathologist specialising in gynaecological tumours.

Signet-ring cell adenocarcinomas are a very rare subtype of mucinous adenocarcinoma [7,8]. In 2016, Sal et al. counted just 19 cases described in the literature [9], and we describe two more here. The pure form is considered exceptional because SRC adenocarcinomas are overwhelmingly associated with other types of adenocarcinoma [10]. One of our cases was a classical endocervical adenocarcinoma associated with an in-situ SRC adenocarcinoma and the other was a pure invasive SRC-type adenocarcinoma.

The average age of the patients in this study was 42 years. There are no points of comparison in the literature for mucinous adenocarcinomas overall. In terms of subtypes however, the patients with non-MD G-type adenocarcinomas in the present study had a mean age of 42 years versus 49 years in the studies of Karamurzin et al. (27 cases) and Kojima et al. (16 cases) [11,12]. All these patients in our study were premenopausal. The patients with MD adenocarcinomas in our study had a similar average age (52 years) as those in Hirai et al.'s study (6 cases; mean age, 53.3 years) [13] and Karamurzin et al.'s (13 cases; mean age, 49.8 years) [11], but were older on average than those in Gilks et al.'s study (26 cases; mean age, 42 years) [14]. For I-type adenocarcinomas, the mean age of the patients in our study was 37 years, which is in contradiction with Howitt et al.'s finding that patients with I-type adenocarcinomas in situ were on average older (44.5 years) than those with classical adenocarcinomas in situ (32.6 years) [15]. Finally, the two patients in our study with SRC adenocarcinomas were young (29 and 42 years old), which is in keeping with the average age of 46.2 years found in a review of 19 cases [9].

In terms of symptoms, the 10 patients with a G-type adenocarcinoma mainly had metrorrhagia, mucinous vaginal discharge and pelvic pain, as described previously [13,14,16,17]. The most common symptom for patients with I-type adenocarcinomas was metrorrhagia [18]. This was presented by one of the six patients with an I-type adenocarcinoma; the five others were asymptomatic. The most frequent symptom of SRC adenocarcinoma was metrorrhagia, as presented by both the patients in our study, one of whom also reported mucinous discharge. Two of the patients with a G-type adenocarcinoma had previously had a borderline mucinous ovarian tumour, an association previously reported by Gilks et al. [14].

Cervical smears can allow some mucinous adenocarcinomas of the cervix to be diagnosed. This was not the case for our patients: 13 of the 18 available cervical smears were abnormal but did not lead to a diagnosis of mucinous adenocarcinoma. For MD adenocarcinomas, cytology samples are not always informative because of a poor diagnostic sensitivity for some authors [14,17] whereas others describe precise cytological criteria [13,19]. Preoperative diagnosis of a MD adenocarcinoma is difficult because the high location of the lesions in the endocervix means that biopsies are rarely informative [17]. Likewise, just one of the six I-type adenocarcinomas in this study was diagnosed before surgery. Histological diagnosis is difficult because I-type adenocarcinomas can resemble benign endocervical glands [20], a colorectal adenocarcinoma, or a metastasis [21,22]. For the two patients with SRC adenocarcinomas, their cervical smears revealed atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions or atypical glandular cells, as described previously by various authors [23]. Overall, cervical biopsies were diagnostic in just 39% of the cases in this study.

The morphological aspect of the tumours was as described in the WHO classification [5]. Ovarian invasion was observed for two patients with a non-MD G-type adenocarcinoma, as described by Mikami et al. [24]. The available immunohistochemical data were consistent with those in the literature, with carcinoembryonic antigen (CEA) positivity in 75% of cases, as reported by Carleton et al. [25] ; and negative p16 staining in most cases (83%), as in Kojima et al. [12] (88%) and to a lesser extent Mikami et al. [26] (70%). All hormone receptor tests were negative, CK7 staining was positive in all cases and CK20 in half, also as described previously [11,25]. Among the four cases of MD adenocarcinoma, CEA markers were positive for two, a slightly lower proportion than reported by Carleton et al. [25]; p16 staining was negative in three cases and focally positive in one; and the hormone receptor tests were all negative, as reported previously [22,25,26]. Lee et al.'s meta-analysis shows that CEA, Claudin 18 and loss of ER expression in the lesional nuclei are useful to differentiate MD and non MD G-type adenocarcinomas from a normal/benign endocervix. They also found that HIK1083 was useful to compare them with benign endocervical and endometrioid lesions [27]. All the I-type adenocarcinomas were p16 positive and the two that were tested were also CEA positive, in keeping with previous studies [11,21,28]. Immunohistochemical data were only available for one of the two SRC adenocarcinomas. In keeping with the literature, it was p16 and CK7 positive, with negative hormone receptor tests [9,21,28].

Gastric type adenocarcinomas are usually described as HPV negative [24,26,29–31]. The HPV status was only available for two of our ten cases: one MD adenocarcinoma was HPV positive and one non-MD G-type adenocarcinoma was HPV negative. Three of the patients with an I-type adenocarcinoma were HPV positive, which is consistent with the analyses of several groups pointing towards intestinal subtypes being associated with HPV, although this remains controversial [5,11,15,22,31]. Signet-ring cell adenocarcinomas can be HPV positive, especially for HPV 18 [9,23]. The only SRC adenocarcinoma case whose HPV status was recorded was positive for several HPV oncogenes, including type 18.

To our knowledge, our study is the first to report radiographic results for I-type adenocarcinomas and ultrasound descriptions of non-MD G-type adenocarcinomas. Magnetic resonance imaging for the latter showed heterogeneous cervical enlargement with T2 hyperintensity, similar to Tsuboyama et al.'s observations [32]. The one set of ultrasound images for an MD adenocarcinoma showed the typical aspect described by Lim et al. [17] and Park et al. [33]: a

multilocular cystic mass, in some cases hypervascular on Doppler sonography. Magnetic resonance imaging has been described as the most effective tool for the radiographic diagnosis of MD adenocarcinoma [34,35]. It was diagnostic in three of our four cases. The radiographic aspect of malignant adenocarcinomas can be misleading, being similar to that of benign nabothian cysts [17,36]. The three MRI reports for patients with I-type adenocarcinomas suggest that they have the typical MRI aspect of mucinous adenocarcinomas. One of the two patients with a SRC adenocarcinoma had a PET scan. This exam is crucial to exclude cervical metastasis of a primary gastric, gallbladder, breast, lung or ovarian cancer [9,23,37–39].

In our study group, the patients with non-MD G-type adenocarcinomas had better outcomes than reported previously in the literature for these types of tumour [11,12,16], but theirs were at an early stage. Minimal deviation adenocarcinomas are also associated with a negative prognosis [12,14], but this relates to advanced stages. As described previously by Hirai et al. [13] and Lim et al. [17], their prognosis is not always negative if the adenocarcinoma is diagnosed early. In their meta-analysis of 347 cases, Li et al. emphasise the importance of surgical treatment, followed for advanced stages by radiochemotherapy [40].

The evolution towards peritoneal carcinomatosis is a known feature of mucinous adenocarcinomas [41]. In this study, four patients developed peritoneal carcinomatosis, of which three had a G-type mucinous adenocarcinoma. All the patients in our series with I-type adenocarcinomas had remission, after 27 months on average. The crucial issues with these adenocarcinomas is to distinguish them from endocervical glands and from a non-cervical primary location, which affect prognosis and management. The prognosis of patients with SRC adenocarcinomas is not known because of the rarity of these tumours, but existing results suggest they are poorly radio- and chemosensitive [19,42,43]. One of the women in this study progressed under concomitant radiochemotherapy. The other patient died from the disease after a recurrence 7 years after the initial treatment. These results suggest that this subtype is particularly aggressive.

In their meta-analysis, He et al. [44] suggest that neoadjuvant chemotherapy (based on platinum as the primary drug) may be useful for cervical cancers with FIGO stages IB-IIB, because the high response increases operability, for both squamous or non-squamous carcinomas. However, they report that the long-term efficacy of the treatment, based on overall survival and progression-free survival, is increased in patients with squamous cell carcinomas, especially for those with FIGO stages greater than IIB [44].

Mucinous adenocarcinomas are currently treated in the same way as other forms of cervical cancer with surgery as a first treatment for early stages and concomitant radiochemotherapy for more advanced tumours. The drugs usually used for radiochemotherapy are cisplatin alone, or cisplatin associated with 5-fluorouracil, administrated during external beam radiotherapy. In case of metastatic disease or relapse, cisplatin-based chemotherapy is usually administrated, and can be associated with paclitaxel and bevacizumab, with numerous alternatives (for example cisplatin/paclitaxel, topotecan/paclitaxel/bevacizumab, carboplatin/paclitaxel with or without bevacizumab, or cisplatin/topotecan).

Radical treatment is typically recommended for these aggressive forms of cancer, which affect young women of childbearing age. A precise analysis of the different subtypes may allow specific treatment protocols to be developed.

An immunohistochemical study of cervical mucinous adenocarcinomas should improve the diagnosis of these rare cancers.

Declarations of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

The translation of this article was supported by the Bibliothèque Scientifique de l'Internat de Lyon and the Hospices Civils de Lyon.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jogoh.2019.02.002.

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