Rare disease

Mesonephric adenocarcinoma of the uterine cervix and literature review

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Summary

Mesonephric adenocarcinoma is a rare type of cervical cancer that derives from mesonephric remnants in the uterine cervix. To the best of our knowledge, this is the 34th case of mesonephric adenocarcinoma in adult women documented in the literature. We present an asymptomatic 64-year-old postmenopausal woman presenting with a suspicious-looking cervix as an incidental finding and diagnosed with a stage IB mesonephric adenocarcinoma of the cervix. This case was managed with radical hysterectomy, bilateral salpingoophorectomy and pelvic lymphadenectomy. The rarity of such cases imposes challenges on the management in terms of diagnosis, prognosis and therapeutic options.

BACKGROUND

Mesonephric carcinomas are a distinct subtype of epithelial tumours of the uterine cervix which derive from the remnants of the paired mesonephric (Wolff's) ducts.¹

Mesonephric remnants can be present in 22% of uterine cervixes in adults.²

The incidence of such neoplasms is difficult to determine due to *rarity*, *previous misclassification* of clear cell carcinomas and yolk sac tumours as mesonephric carcinomas and *potential underreporting due to misclassification* of mesonephric carcinoma as müllerian tumours or mesonephric hyperplasia.³

The evidence regarding the clinical course, prognosis and optimal treatment is limited.

CASE PRESENTATION

An asymptomatic 64-year-old patient was referred to colposcopy services, by her general practitioner with the indication of a suspicious-looking cervix during routine cervical smear. Her previous obstetric history included that of four vaginal births and the gynaecological that of menopause since the age of 50. Her medical history included hypothyroidism on thyroxine, asthma, osteoporosis and smoking. She also had a history of breast cancer treated with mastectomy and chemoradiation 8 years before.

Colposcopy gave the impression of invasive disease and directed cervical punch biopsies revealed closely packed dilated mucin-filled glands with an attenuated epithelial lining which was focally positive for cytokeratin 7 (CK7). CK20, gross cystic disease fluid protein (GCDFP), thyroid transcription factor-1 (TTF1) and thyroglobulin were negative. These features were considered as consistent with a cervical mucinous lesion. No malignant features were evident but further evaluation was recommended. The cervical smear was normal.

The case was referred to the gynaecology multidisciplinary team and the suggestion was that of examination

under anaesthesia, cystoscopy and cervical cone biopsy. The examination under anaesthesia and cystoscopy revealed an unusually indurated cervix.

The knife cone biopsy measures 22 × 13 and 18 mm in depth, and microscopically showed a diffusely infiltrating tumour composed of groups of dilated glands with minimal atypia. The tumour incompletely was excised and was present at one side of the cervical canal and measuring 20 × 9 × 7 mm. No lympho-vascular invasion was identified and the squamous epithelium and endocervical glands were normal.

Immunohistochemical staining was positive for cytokeratin (pan cytokeratin) AE1/AE3, epithelial membrane antigen (EMA), E cadherin and vimentin. CD10 was focally positive and with only occasional cells positive for calretinin. The tumour was negative for monoclonal carcino embryonic antigen (mCEA), CK20, TTF1, thyroglobulin and GCDFP (figures 1–3).

The features were considered to be suggestive of a well-differentiated mesonephric adenocarcinoma of the cervix.

MRI was normal and the staging was that of T1N0M0.

Radical hysterectomy specimen confirmed an International Federation of Gynecology and Obstetrics (FIGO) IB1 (with a maximum horizontal/depth tumour dimensions of 15/5 mm), well-differentiated adenocarcinoma with negative nodes ($n = 19$) and clear margins, with no lymphovascular space invasion (LVSI).

Staging with MRI scan took place before a radical hysterectomy, and bilateral salpingoophorectomy along with pelvic lymphadenectomy confirmed an IB1 well-differentiated mesonephric adenocarcinoma with negative pelvic nodes.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included the more common well-differentiated villoglandular adenocarcinoma of cervix, adenoma malignum, endometrioid adenocarcinoma, clear cell carcinoma and mesonephric hyperplasia.⁴

Figure 1 Histology showed closely packed glands, lined by cuboidal epithelium with minimal to mild cytological atypia. Some glands are dilated and are filled with eosinophilic secretions. Mesonephric duct hyperplasia was seen elsewhere in the specimen (H&E).

TREATMENT

This case was managed with radical hysterectomy, bilateral salpingoophorectomy and pelvic lymphadenectomy.

OUTCOME AND FOLLOW-UP

Recovery from surgery was uneventful and the patient has remained disease-free for 6 months.

DISCUSSION

The presenting symptom is most commonly abnormal uterine bleeding. Many cases are diagnosed as an incidental finding on cervical cone or hysterectomy specimen. Examination revealed a cervical mass in many of these cases.

Age range at presentation is between 24 and 73 years with a mean of 50.7.

Unlike the case of the more common squamous epithelial carcinoma, it is rarely presenting with the abnormal cervical smear result, has more advanced age at presentation and its incidence does not appear to decline with age.

Figure 2 Strong positivity for Pan-cytokeratin AE1/3 staining.

Figure 3 Strong positivity for vimentin staining.

The diagnosis has been supported by endometrial curettings, directed/cone cervical biopsies and hysterectomy specimens.

A common finding on endometrial biopsies is endometrioid adenocarcinoma.

The microscopic appearance can be characterised by the *predominant pattern*. More common patterns are the *tubular*, which needs to be distinguished from diffuse mesonephric hyperplasia, and the *ductal* pattern, which needs to be distinguished from endometrioid adenocarcinomas of cervix and its minimal deviation variant. *Malignant spindle cell biphasic pattern* (malignant mixed mesonephric tumour, MMMT) should be differentiated from primary MMMT of cervix. Focal *retiform* and *sex-cord-like* patterns are more common in adnexal tumours deriving from remnants of upper Wolffian duct.⁵

These neoplasms tend to be adjacent to areas of mesonephric glandular hyperplasia.⁶

Mesonephric remnant hyperplasia, even with deep infiltrating and diffuse hyperplastic appearance, is not related to poor prognosis and needs to be distinguished from malignant lesions.⁷ Discriminating features of adenocarcinoma are nuclear atypia, increased mitotic activity (>10/HPFs) (high power field), lymphovascular space invasion and necrotic luminal debris. Ki immunostain may also prove useful in differentiating.³

Immunohistochemical features of mesonephric adenocarcinoma include positivity for CK7, CAM5.2, EMA and reactivity for CD10, calretinin and vimentin. Carcinoembryonic antigen (CEA), CK20, ER and PR are usually negative.⁷ As expected, immunoreactivity for p16 is negative, thus not linking these tumours with high-risk human papillomavirus infection.⁸ Immunoreactivity for PAX2 seems to be absent in mesonephric adenocarcinoma and cervical adenocarcinoma along with its minimal deviation variant, but is diffusely positive in mesonephric hyperplasia.⁹

Owing to the small number of cases with adequate follow-up, prognosis cannot be accurately predicted. The vast majority of patients with cervical adenocarcinoma of mesonephric origin diagnosed at a stage IB and had a mean disease-free interval of 48.6 months. Recurrence rate was 23% (6 of 26 patients), with a mean interval of 40 (7–74) months and stage of disease was IB in three of

Table 1 Clinicopathological characteristics of cases^{3, 4, 5, 8, 9, 10, 11, 13}

Cases reported author/year	Age	Presenting symptom	Immunocytochemistry		Primary treatment	Adjuvant treatment	Stage	Recurrence treatment and outcome in months
			Positive	Negative				
Adenocarcinomas								
1. This case/2012	64	None	AE1/AE3 EMA E cadherin, vimentin, CK7, CD10 focally, calretinine occasional cells	CEA, CK20, TTF1, GCDFP	RAH/BSO pelvic N	None	IB No LVSI	None at 6
2. Fukunanga/2007	46	Irregular vaginal bleeding/suspicious Cx	CAM5.2 CK7, EMA, p53 chromogranine focal, calretinine occasional cells	CEA, CD10 synaptophysin vimentin oestrogen progesterone	TAH/BSO, pelvis N omentectomy	None	IB	None at 4
3. Stephanie Yap/2006	54	PMB	CK7, CAM5.2 EMA	Chromograin synaptophysin CD10, CEA vimentin, inhibin calretinine, oestrogen	RAH/BSO aortic/pelvic N	RT external beam 5040 cGy + intracav. 1275 cGY	IB, LVSI	None at 37
4. Angeles/2004 ⁴	47	HMB pelvic mass	AE1/AE3 CK7, CK19, EMA, Ca125 oestrogen progesterone CD10 focal		TAH/BSO	RT caesium implants	IB	None at 12
5. Bagué <i>et al</i> /2004 case 1	41	AUB		α -Inhibin	TAH, BSO, pelvic N app	RT	IB1	None at 137
6. Bagué <i>et al</i> /2004 ¹⁰ case 3	24	N/A		α -Inhibin	N/A	N/A	IIA	N/A
7. Bagué <i>et al</i> /2004 ¹⁰ case 4	45	PCB	Vimentin focal CD10 focal	α -Inhibin	TAH, USO	None	IB1	None at 37
8. Silver <i>et al</i> /2001 ³ case 1	62	PMB	AE1/3, CK1, EMA, CK7difuse	CK20, ER/PR, mCEA	TAH, BSO	None	IB	None at 18
9. Silver <i>et al</i> /2001 ³ case 2	47	Uterine prolapse	AE1/3, CK1, EMA, CK7difuse	CK20, ER/PR, mCEA	TAH, BSO	None	IB	None at 25
10. Silver <i>et al</i> /2001 ³ case 3	40	CIN in smear	AE1/3, CK1, EMA, CK7difuse	CK20, ER/PR, mCEA	TAH, BSO	None	IB	None at 38
11. Silver <i>et al</i> /2001 ³ case 4	54	PMB	AE1/3, CK1, EMA, CK7difuse	CK20, ER/PR, mCEA	TAH, BSO	None	IB	None at 73
12. Silver <i>et al</i> /2001 ³ case 5	67	PMB	AE1/3, CK1, EMA, CK7difuse	CK20, ER/PR, mCEA	TAH, BSO	None	IB	None at 100
13. Silver <i>et al</i> /2001 ³ case 6	72	AGUS on smear	AE1/3, CK1, EMA, CK7difuse	CK20, ER/PR, mCEA	TAH, BSO, pelvic N	RT	IB, vaginal cuff	Rectovaginal at 20, ChemoT, none at 30
14. Silver <i>et al</i> /2001 ³ case 8	62	PMB, endometrial Ca on curete	AE1/3, CK1, EMA, CK7difuse	CK20, ER/PR, mCEA	TAH, BSO, pelvic N	None	IB	N/A
15. Silver <i>et al</i> /2001 ³ case 9	56	Rt ovarian cystadenoma	AE1/3, CK1, EMA, CK7difuse	CK20, ER/PR, mCEA	TAH, BSO,	None	N/A	None at 89
16. Silver <i>et al</i> /2001 ³ case 10	35	AUB pelvic pain	AE1/3, CK1, EMA, CK7difuse	CK20, ER/PR, mCEA	Pelvic RT		IIB	Pelvis at 26, ChemoT, DOD at 38
17. Clement <i>et al</i> /1995 ⁵ case 1	46	HMB/fibroid	EMA, vimentin		TAH, BSO, pelvic N	N/A	IB, (+)pelvic N	None at 24
18. Clement <i>et al</i> /1995 ⁵ case 2	34	HMB	EMA, vimentin		TAH, BSO	N/A	IB, (+)pelvic N	Abdomen at 12, Chemo, none at 24
	71	AdenoCA on smear, pelvic mass	EMA, vimentin		TAH, BSO, pelvic N	RT	IB + endometrioid adenoCA	

Continued

Table 1 Continued

Cases reported author/year	Age	Presenting symptom	Immunocytochemistry		Primary treatment	Adjuvant treatment	Stage	Recurrence treatment and outcome in months
			Positive	Negative				
19. Clement <i>et al</i> /1995 ⁵ case 3								Abdomen at 4.5, chemo, DOD at 8.5 (concurrent IIC clear cell ovarian carcinoma)
20. Clement <i>et al</i> /1995 ⁵ case 4	67	PMB/Cx mass	EMA, vimentin		TAH, BSO, pelvic N	N/A	IB	N/A
21. Stewart <i>et al</i> /1993 ¹¹	37	HMB/suspicious Cx	CK1, vimentin chromogranin serotonin	CEA	RAH, BSO, pelvic N	None	IB1	None at 120
22. Ferry and Scully/1990 ²	55	Pelvic relaxation	N/A	N/A	Hyst, BSO	RT	N/A	None at 60
23. Lang <i>et al</i> /1990 case 2	55	N/A	N/A	N/A	TAH	N/A	IB	N/A
24. Valente and Susin 1987 ¹²	58	PMB	N/A	N/A	RAH, BSO, pelvic N	None	IB1	Pelvis, RT, DOD at 28
25. Buntine/1979 ¹³	48	Fibroids	N/A	N/A	TAH, BSO	None	N/A	Vaginal at 84, RT, DOD at 108
26. Mc Gee/1962	36	PCB	N/A	N/A	TAH	None	IB	Pelvis at 72, None, 84
Malignant mixed mesonephric tumours								
27. Bagué <i>et al</i> /2004 ¹⁰ case 6	54	AUB	Vimentine	α -Inhibin	TAH, BSO, PelvicN omentum	None	IIA MMMT	Bowel, DOD AT 7
28. Bagué <i>et al</i> /2004 ¹⁰ case 8	62	N/A	Vimentine	α -Inhibin	TAH, BSO	ChemoRT	IVB	Bone, AWD at 40
29. Bagué <i>et al</i> /2004 ¹⁰ case 9	54	N/A	Vimentine calretinin focal	α -Inhibin	TAH, BSO, Pelvic N omentum	None	IB1	None at 13
30. Silver <i>et al</i> /2001 ³ case 7	39	Menorrhagia, Cx fibroid	AE1/3, CK1, EMA, CK7diffuse	CK20, ER/PR mCEA	TAH, BSO	RT	IB MMMT	Mediastinum at 67, chemo, DOD 74
31. Silver <i>et al</i> /2001 ³ case 11	43	AUB	AE1/3, CK1, EMA, CK7diffuse	CK20, ER/PR mCEA	TAH, BSO, Pelvic N omentum, subphrenic mass	Chemo	IVB MMMT	Bladder/pelvis at 8, RT DOD at 9
32. Clement <i>et al</i> /1995 ⁵ case 5	37	PCB	EMA, vimentin SMA, CK1 focal		TAH, BSO, Pelvic N	Chemo	IB MMMT	Abdo at 108, surgery and chemo, omental/hepatic/bone 132, chemo, AWD at 156
33. Clement <i>et al</i> /1995 ⁵ case 6	73	PMB	EMA, vimentin SMA, CK1 focal		TAH, BSO	RT	IB, MMMT	None at 36
34. Clement <i>et al</i> /1995 ⁵	39	AUB	EMA, vimentin		TAH, BSO	N/A	IB	N/A

AE1, pan cytokeratine; AGUS, abnormal glandular cells of undetermined significance; AUB, abnormal uterine bleeding; AWD, alive with disease; BSO, bilateral salpingoophorectomy; CAM, low molecular weight cytokeratine; CD10; CEA, carcino embryonic antigen; ChemoT, chemotherapy; CIN, cervical intraepithelial neoplasia; CK20, cytokeratin 20; Cx, uterine cervix; DOD, died of disease; EMA, epithelial membrane antigen; ER/PR, estrogen receptor/progesterone receptor; FP; GCDFP, gross cystic disease fluid protein; HMB, heavy menstrual bleeding; IB No; IIA, stage IIA; LVSI, lymphovascular space invasion; mCEA, monoclonal carcinoembryonic antigen; MMMT, malignant mesonephric mixed; N, lymph nodes; N/A, not available; PCB, post coital bleeding; PMB, post menopausal bleeding; RAH, radical abdominal hysterectomy; RT, radiotherapy; TAH, total abdominal hysterectomy; TTF1, thyroid transcription factor-1.

them, above IB in two of them and unknown in one of these six patients. Two patients (7.6%) died of disease at 28 and 38 months.

Out of the eight patients with MMMTs, five were diagnosed at stage IB and three above IB. Five of these eight patients (62.5%) had a recurrence with a mean disease-free interval of 46 months, whereas 2 of 8 (25%) died of the disease at 7 and 74 months.

Out of 34 patients, 15 had lymphadenectomy and positive lymph nodes were found on 3 of them (2 of 7 patients with MMT and 1 of 27 patients with adenocarcinoma).

It appears that the MMMTs are more aggressive since they were diagnosed at a more advanced stage and had worse outcomes.

All the patients except one were treated with hysterectomy as the primary treatment.

Advanced stage disease of adenocarcinoma seemed to respond to radiotherapy, but for the MMMTs the combination of chemotherapy with radiotherapy appears to be preferable.

A summary of the cases reported in the literature so far is presented in Table 1.^{3 5–7 10–13}

Learning point

- Though the incidence of such tumour is rare, one should consider the above diagnosis in cervical tumours presenting the characteristics mentioned above.

Competing interests None.

Patient consent Obtained.

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