Misdiagnosed mesonephric adenocarcinoma in the cervix: a case report and review of the literature

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Case Report

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Abstract

Background Mesonephric adenocarcinoma (MNAC) in the female reproductive system is a rare tumour caused by remnants of the mesonephric duct, mainly located in the cervix. Because of the rarity of the disease and few reports to date, no specific clinical features have been identified. Its diagnosis is challenging because MNAC may exhibit multiple morphological patterns, complicating differential diagnosis.

Case presentation We report a 57-year-old female with cervical MNAC who was misdiagnosed with squamous cell carcinoma by biopsy. Histological study revealed a solid, glandular and papillary tumour. The pattern of papillary growth exhibited a vascular axis, and the morphology was similar to that of high-grade squamous intraepithelial lesions. Based on immunohistochemistry, the tumour cells were negative for CK5/6, P40 and Vimentin; GATA-binding protein 3 (GATA3), CD10, AE1/AE3, CK7 and P16 were diffusely positive; calretinin was focally positive; and oestrogen receptor (ER), progesterone receptor (PR), thyroid transcription factor-1 (TTF1) and p53 were negative. The patient received neoadjuvant chemotherapy, surgery and adjuvant chemotherapy and had no evidence of disease as of 10 months after the operation. The clinical manifestations, pathological features, treatment and prognosis of MNAC were summarized by reviewing the existing literature.

Conclusions When tumours with papillary and squamous epithelial growth patterns are detected by biopsy, it is necessary to apply immunohistochemistry analysis to avoid misdiagnosis.

Background

Mesonephric adenocarcinoma (MNAC) is a rare malignant tumour derived from remnants of the mesonephric duct in the female genital tract. MNAC usually occurs in the cervix [1], vagina [2], uterine body [3] and ovary [4]. In males, the mesonephric ducts give rise to the testes, epididymis, vas deferens, seminal vesicles, and ejaculatory ducts, whereas the mesonephric ducts are degenerative in females. However, in females, mesonephric remains are usually present in the stroma of the cervix, adjacent to the ovaries, fallopian tubes, and broad ligaments, though they rarely occur in the vaginal wall or myometrium [3]. Mesonephric carcinoma is presumed to originate from these remnants.

The most common clinical manifestation of MANC is vaginal haemorrhage. Due to the rarity of this disease, its aetiology and precursor lesions remain unclear. All MNAC patients reported thus far underwent surgical resection. Adjuvant radiotherapy and chemotherapy are often used in patients with advanced disease, but the best scheme and effect of treatment are unknown [5]. The histopathological features of MNAC are the combination of multiple growth patterns, showing tubular, glandular, papillary and glomerular-like structures. Overall, the pathogenesis of mesonephric adenocarcinoma remains unclear. MNAC shows preserved wild-type p53 expression patterns, diffuse expression patterns for CD10, GATA-binding protein 3 (GATA3) and paired box 2 (PAX2), and negative reactivity for hormonal receptors [6-8]. These findings indicate that MNAC may have immunohistochemical and molecular biological

characteristics that differ from those of endometrioid carcinoma, serous carcinoma and cervical adenocarcinoma. According to the report of targeted genomic analysis using next-generation sequencing (NGS), most MNACs harbour KRAS mutations [3,9], suggesting that KRAS mutations are related to the development of MNAC. Although some researchers believe that the prognosis of MNAC is better than that of other tumours [10], others emphasize the aggressive behaviour of this tumour [11].

Because of the limitation of preoperative biopsy, MNAC may be easily misdiagnosed based on clinical or pathological diagnosis. In this paper, the clinical and pathological features of MNAC (misdiagnosed as squamous cell carcinoma by biopsy) were analysed retrospectively to improve our understanding of the disease.

Case Presentation

The patient was a 57-year-old female with vaginal bleeding, less than the menstrual volume, and no abdominal pain. A magnetic resonance imaging (MRI) scan revealed a 3.2 cm-diameter mass in the right anterior wall of the cervix, with high T1 and T2 signals; diffusion-weighted imaging (DWI) showed high signal intensity, and the arterial phase was significantly intensified after enhancement. Ultrasound imaging revealed an irregular hypoechoic area in the cervix, with uneven internal echo and abundant blood flow signals. The first laboratory workup showed an increased CA125 level of 56.29 U/mL. To confirm the diagnosis, biopsy revealed that the tumour was solid and papillary, with a microvascular axis; the morphology of the tumour was similar to that of squamous cell carcinoma without keratosis (Fig. 1A and Fig. 1B). The lesion was misdiagnosed as squamous cell carcinoma due to the morphology displaying the squamous cell growth pattern and the lack of immunohistochemistry. As MRI showed that the tumour invaded the parauterine tissue, a course of neoadjuvant therapy (combination of irinotecan and nedaplatin) was carried out prior to surgery of radical hysterectomy, radical hysterectomy and lymphadenectomy. Before the operation, the level of CA125 was reduced to 37.17 U/ml. Grossly, a 2.9×2.9×2.7-cm ulcerative mass was located in the cervix, invading the upper 1/3 of the vagina. The uterine body, ovaries and fallopian tubes were unremarkable.

Microscopically, the mass shows a variety of architectural growth patterns, including solid (Fig. 2A), glandular (Fig. 2B) and papillary (Fig. 2C) patterns. The pattern of papillary growth has a vascular axis, and the morphology is similar to that of high-grade squamous intraepithelial lesions (Fig. 2C). Spindle-like epithelial cells can be seen around the glandular structure; the nucleus is round and oval, and the nucleolus is not obvious (Fig. 2B). Tumour thrombus were found in vessels around the tumour, and perineural infiltration was not identified (Fig. 2D). Immunohistochemical studies of the tumour cells yielded the following results: negative for CK5/6 (Fig. 3A), p40 (Fig. 3B) and Vimentin (Fig. 3C); GATA3 (Fig. 3D), CD10 (Fig. 3E), AE1/AE3 (Fig. 3F), CK7 and p16 (Fig. 3G) diffusely positive; calretinin focally positive; oestrogen receptor (ER), progesterone receptor (PR), thyroid transcription factor-1 (TTF1) and p53 negative. No metastasis was found in any of the lymph nodes. According to the International Federation of Gynecology and Obstetrics (FIGO) stage of the American Joint Committee on Cancer (AJCC) 8th Edition, the stage of the tumour was IIA1. The patient received postoperative chemotherapy

(combination of irinotecan and nedaplatin) and had no evidence of disease as of 10 months after the operation.

Discussion

Mesonephric duct remnants in the cervix are found in approximately 22% of adult females [12]. However, tumours from mesonephric remnants rarely occur in the female genital tract. Nogales divided the mesonephric ducts into two distinct regions: an upper zone, including the rete ovarii; and a lower zone, containing the cervix and vagina [13]. Tumours in these areas are usually morphologically distinct. As early as 1939, Schiller named the mesonephric duct tumour as mesonephroma [14]. Then, researchers reported several cases that were histologically similar to the tumor Schiller reported [15-17]. Herbst and Scully reported clear cell carcinoma of the vagina and suggested that it originated in the Müllerian rather than the mesonephric duct [18]. However, Allyn et al reported 36 cases of mesonephric tumours in the vagina and proposed that mesonephric tumours should be classified into 2 types: endodermal sinus tumours and clear cell carcinomas [19]. To date, so-called mesonephroma is usually referred to as mesonephric carcinoma or mesonephric adenocarcinoma.

Mesonephric adenocarcinoma is a rare malignant tumour in the female reproductive tract that originates from the remnants of the mesonephric duct. To the best of our knowledge, 55 cases of cervical MNAC have been reported in the literature (Table 1). Among the 55 cases reviewed in this paper, ages ranged from 24 to 76 years, with an average age of 54.2 years. The most common clinical manifestation of MNAC is abnormal vaginal bleeding [5]. Among cases, 19 had vaginal bleeding, including 13 cases of postmenopausal vaginal bleeding and 8 cases of menorrhagia. The most common histological type was adenocarcinoma (49/55), of which 4/49 cases had spindle cell components, 5 cases were malignant mesonephric mixed tumours (MMMTs), and 1 case was mixed adenoneuroendocrine carcinoma (MNAC + NEC). Follow-up information was available for 37 patients; 6 (16%) died of the disease, 7 (19%) were alive with the disease, and 24 (65%) had no evidence of the disease.

The mesonephric remnants of the cervix have been incidentally found during uterectomy. The remnants occasionally proliferate but rarely develop into MNAC. At present, five types of cervical mesonephric lesions have been reported: mesonephric remnants, lobular mesonephric hyperplasia, diffuse mesonephric hyperplasia, mesonephric ductal hyperplasia, and mesonephric carcinoma [20]. Mesonephric remnants usually comprise a ductal structure covered by a single layer of ciliated cuboidal epithelium. Eosinophilic secretion is found in the lumen. Mesonephric hyperplasia can be divided into three categories according to the microscopic morphology: lobular hyperplasia, diffuse hyperplasia, and ductal hyperplasia. It is easy to misdiagnose adenocarcinoma when the number of mesonephric tubes is large and dispersed, but the luminal cells show no atypia or mitoses. The lobular and ductal hyperplasia types are common, but diffuse hyperplasia is rare. Ductal hyperplasia is characterized by large ducts, and microscopic papillary changes are often seen in the epithelium [21,22].

The diagnosis of MNAC is challenging, especially for biopsy materials and frozen sections. Because of the papillary, solid components and squamous epithelial growth pattern, the lesion is often misdiagnosed as a high-grade carcinoma, such as clear cell carcinoma, serous carcinoma, squamous cell carcinoma or carcinosarcoma. Various morphologic patterns can be seen in MNAC, such as tubular, glandular, papillary and reticular patterns. The histologic features of our case were solid and squamous epithelial growth patterns. Initially, the tumour was misdiagnosed as squamous cell carcinoma due to the absence of immunohistochemistry analysis. The differential diagnosis of MNAC depends on its location and microscopic appearance. The diagnosis is easily made when mesonephric remnants and/or hyperplasia are found near the tumour. However, when the tumour shows a complete or major tubular growth pattern, it should be distinguished from diffuse mesonephric hyperplasia. The crowded growth pattern of glands, malignant nuclear features and presence of perineural or vascular invasion support the diagnosis of carcinoma. When MNAC grows into the lateral wall of the uterus, the differential diagnosis includes endometrial-like carcinoma, serous carcinoma, clear cell carcinoma, endometrial stromal tumour and MMMT. MNAC is particularly easy to confuse with clear cell carcinoma. Clear cell adenocarcinoma of the cervix and vagina usually occurs in young women treated with diethylstilbestrol and displays varying degrees of cystic, papillary, clear cells and nail cells. These features are not common in MNAC. In addition, MNAC may exhibit smooth muscle or endometrial stromal differentiation and express desmin and actin. The differential diagnosis of MNAC includes endometrial stromal nodules and low-grade stromal sarcoma. Although the latter tumour may show a tubular or nest pattern, it is characterized by a uniform distribution of cells, such as proliferative endometrial stromal cells, with fine vascularization and vascular space invasion, characteristics not found in MNAC.

The immunochemical features of MNAC usually include diffusely and strongly positive for CD10, CK7, and EMA. PAX8 is strongly expressed in both benign and malignant mesonephric lesions, whereas PAX8 is expressed in various ways in common pathological types of cervical adenocarcinoma. Because PAX8 is expressed in many types of cervical lesions, it is not reliable for differentiating between benign and malignant cervical lesions [23]. PAX2 expression is often absent in MNAC and cervical adenocarcinoma, but PAX2 is diffusely positive in mesonephric hyperplasia, which can be employed as an important way to distinguish mesonephric hyperplasia and MNAC [24]. Other markers, including calretinin, inhibin and androgen receptor (AR), show varying positivity. CEA and CK20 exhibit negative expression patterns. In mesonephric adenocarcinoma, ER and PR are negative or locally positive [25-27]. GATA3, a transcription factor that plays an important role in embryogenesis development and differentiation, is highly sensitive and specific for mesonephric lesions. Because it is positive in all mesonephric remnants, hyperplasia and MNAC and rarely or not expressed in cervical adenocarcinoma, expression of GATA3 may be a marker of mesonephric lesions [28-30]. In addition, TTF-1 may be positive in mesonephric adenocarcinoma, though it is generally considered a biomarker of lung cancer and thyroid cancer [1]. HNF1 β (hepatocyte nuclear factor 1-beta), a marker of clear cell carcinoma, may also be expressed in MNAC [31].

Chromosome copy number changes have been reported in mesonephric adenocarcinoma. In a series of reports, 1q gain was the most common copy number change in MNAC [9, 3]. Moreover, a gain of 1q is also the most common copy number change in endometrial carcinoma [32]. Therefore, genes at 1q may

play an important role in the occurrence and development of mesonephric adenocarcinoma. According to one study, chromosome 1q21.2, which contains the anti-apoptotic gene MCL1, is focally amplified in approximately 10% of all cancers [33]. With regard to MNAC, current data suggest that 1q and 10q gains may be an indicator of poor prognosis and may increase the risk of metastasis [3, 9]. In addition to chromosome changes, gene mutations are also common in MNAC.

KRAS mutation is the most common molecular change in mesonephric adenocarcinomas. According to one study, 12 of 17 cases were confirmed to have KRAS mutations, and the chromatin remodelling gene ARID1A/B was also frequently mutated (8/17) [9]. Common genetic aberrations such as PTEN and PIK3CA in endometrial carcinoma and other types of cervical adenocarcinoma have not been reported in MNAC. TP53 is a rare mutation in mesonephric adenocarcinoma and other cervical adenocarcinomas, but more than 90% of endometrial serous carcinomas have TP53 aberrations. Therefore, KRAS mutations combined with the lack of PIK3CA, PTEN and TP53 mutations would support the diagnosis of MNAC.

Because cervical MNAC is rare, its biological behaviour and prognosis are not clear. It has been reported that the prognosis of MNAC is worse than that of other histological types: the recurrence rate of stage I MNAC is 32%, whereas that of early cervical adenocarcinoma and cervical squamous cell carcinoma are 16% and 11%, respectively [5, 34]. A retrospective study showed that 15 of 48 cases had recurrences, with an average recurrence time of 2.8 years; the recurrence sites were diverse, most of which involved the pelvic cavity and abdominal cavity, with only 2 cases having lung metastasis [35].

Conclusions

Cervical mesonephric adenocarcinoma is a rare tumour. Cervical lesions are usually detected by biopsy. Because of the limitations of biopsy specimens, the lesions is easy to misdiagnose when the histological morphology of MNAC is close to that of squamous cell carcinoma. The present case was misdiagnosed as squamous cell carcinoma by biopsy. When tumours show papillary and squamous epithelial growth patterns by biopsy, it is necessary to carefully observe whether they have adenoid structures and examine them by immunohistochemistry to avoid misdiagnosis.

Abbreviations

MNAC Mesonephric adenocarcinoma

GATA3 GATA-binding protein 3

ER Oestrogen receptor

PR Progesterone receptor

TTF1 Thyroid transcription factor-1

PAX2 Paired box 2

NGS Next-generation sequencing

MRI Magnetic resonance imaging

DWI Diffusion-weighted imaging

FIGO International Federation of Gynecology and Obstetrics

AJCC American Joint Committee on Cancer

MMMTs Malignant mesonephric mixed tumours

AR Androgen receptor

HNF1 β Hepatocyte nuclear factor 1-beta

Declarations

Authors' contributions

Gao Rui collected the case and wrote the paper. Wang Liping only participated in case collection and Jin Long participated in guiding writing.

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Availability of data and materials

All data generated or analyzed during this case are included within the article.

Ethics approval and consent to participate

This case study was approved by the Institutional Ethics Committee of Fujian Provincial Hospital, Fujian Provincial, China.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations the Table file is available as a download in the Supplementary Files.

Figures

Figure 1

Cervical biopsy: the tumour is solid and papillary, with a microvascular axis; the morphology of the tumour is similar to that of squamous cell carcinoma without keratosis. Magnifications: A, $\times 20$, B, $\times 40$.

Figure 2

Histologic features of the mesonephric adenocarcinoma: the tumour shows a solid growth pattern and infiltrates the cervical myometrium (A); in some areas, the tumour shows glandular pattern (B); the pattern of papillary growth has a vascular axis, and the morphology is similar to that of high-grade squamous intraepithelial lesions (C); tumour thrombus were found in vessels around the tumour (D). Magnifications: A, $\times 20$; B, $\times 100$; C&D, $\times 40$.

Figure 3

Immunohistochemical studies of the tumour cells: negative for CK5/6 (A), p40 (B) and Vimentin (C); GATA3 (D), CD10 (E), AE1/AE3 (F), and p16 (G) diffusely positive. Magnifications: A&B, ×40; C, ×20; E&F&G, ×100.

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