Indian Journal of Gynecologic Oncology (2024) 22:13
https://doi.org/10.1007/s40944-023-00785-7

CASE REPORT

Adenoid Cystic Carcinoma of Cervix: A Rare Entity

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Received: 25 May 2023 / Revised: 13 November 2023 / Accepted: 28 November 2023 / Published online: 6 January 2024

Abstract

Background Adenoid cystic carcinoma is a malignant neoplasm rarely occurring in the uterine cervix. It accounts for less than 1% of all cervical carcinomas.

Case Herein we report a case of Adenoid cystic carcinoma of the cervix in a 41-year-old woman who presented with a 3-month history of bleeding and discharge per vaginum.

Result The patient underwent a biopsy. On histopathological evaluation, the section showed fragments of squamous epithelium with a subepithelial tumor arranged in tubules, anastomosing cords, and sheets. Tumor cells were basaloid with scant cytoplasm and hyperchromatic nucleus. Some of the tubules contained myxoid matrix. The cords were separated by basement membrane like material. On immunohistochemistry, a biphasic tumor was identified composed of luminal epithelial cells highlighted by CK7, CD117, and BerEP4, and the myoepithelial cells highlighted by p63. There was a diffuse nuclear and cytoplasmic expression of the p16 protein. Tumor cells were negative for GATA3, Synaptophysin, Chromogranin, CD56, S100, and PAX8. Based on morphology and immunohistochemistry, a diagnosis of Adenoid cystic carcinoma was considered.

Conclusion Compared to other cervical malignancies, Adenoid cystic carcinoma is exceedingly rare and has an aggressive clinical course with early nodal and distant metastases. Diagnosis is often tedious owing to the rarity and the histological overlap with other neoplasms. We have discussed this case along with a brief review of Adenoid cystic carcinoma of the cervix.

Keywords Adenoid cystic carcinoma · Cervical malignancy · Cervix

Introduction

Adenoid cystic carcinoma (ACC) of the cervix is a rare malignant tumor, originally described by McGee et al. in 1965 [1]. It is a well-recognized entity in the salivary gland but can also originate in other sites that have a secretory gland component such as the ear, sino-nasopharyngeal region, esophagus, bronchus, breast and prostate [2, 3]. ACC accounts for less than 1% of all cervical carcinomas and is seen in the postmenopausal age group [4]. It is important to recognize and report this rare entity due to its aggressive clinical course and propensity to show early loco-regional lymph nodal and distant metastases [4]. Herein we report a case of Adenoid cystic carcinoma of the cervix in a 41-year-old woman.

Case Report

A 41-year-old female presented with chief complaints of intermittent bleeding and foul-smelling vaginal discharge for 3 months. Patient also complained of lower back ache and increased frequency of urination. There was no significant medical or family history. There was a history of tubal ligation. On per speculum examination, there was a large growth replacing the cervix, involving the anterior and left fornix and bled on touch. Ultrasonography revealed a 7 × 6 cm heterogeneous cervical mass with internal vascularity. A biopsy was done. On histopathological evaluation, the section showed fragments of squamous epithelium with a subepithelial tumor arranged in tubules, anastomosing cords,

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and sheets. Tumor cells were basaloid with scant cytoplasm and hyperchromatic nucleus. Some of the tubules contained myxoid matrix (Fig. 1A,B). The cords were separated by basement membrane like material (Fig. 1C). The basement membrane like material was highlighted by PAS stain (Fig. 1D). On immunohistochemistry, a biphasic tumor was identified composed of luminal epithelial cells highlighted by CK7, CD117, and BerEP4, and the myoepithelial cells highlighted by p63. There was a diffuse nuclear and cytoplasmic expression of the p16 protein (Fig. 2). Tumor cells were negative for GATA3, Synaptophysin, Chromogranin, CD56, S100, and PAX8. Based on morphology and immunohistochemistry, a diagnosis of ACC was considered.

Discussion

The earliest description of Adenoid cystic carcinoma of cervix appeared in 1949 by Paalman and Counsel who reported the case as cylindroma [5]. In 1965, McGee et al. introduced

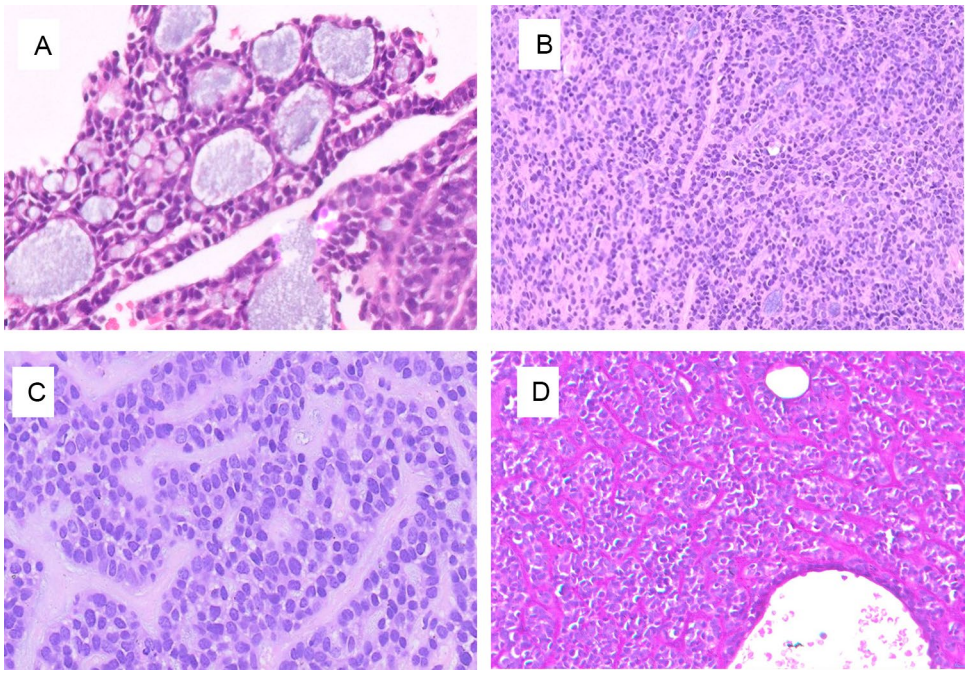

Fig. 1 Histological findings in cervical adenoid cystic carcinoma. **A** H&E (200×) Tumor cells exhibiting tubular pattern with myxoid matrix. **B** H&E (100×) Tumor cells arranged in solid sheets and anastomosing cords. **C** H&E (400×) Myoepithelial cells admixed with basement membrane material **D** PAS (400×) Basement membrane like material is highlighted

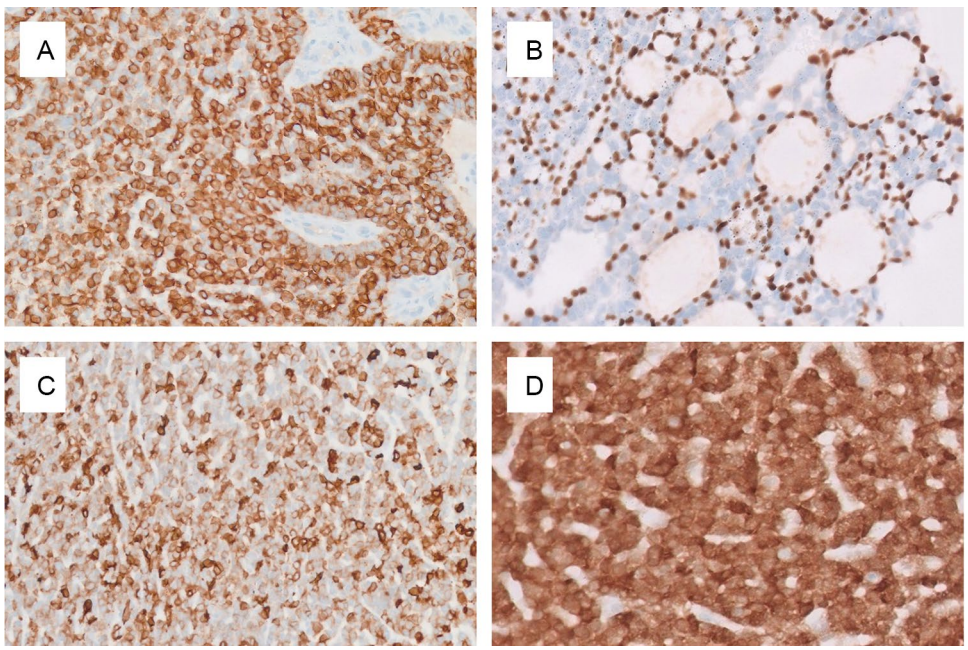

Fig. 2 Immunohistochemical findings in cervical adenoid cystic carcinoma. **A** KRT7 (CK7) highlights luminal cells (200×). **B** p63 highlights abluminal myoepithelial cells (200×). **C** KIT (CD117) expression in luminal cells (200×). **D** Strong nuclear and cytoplasmic expression of p16 protein (200×)

the definition of ACC for previously recognised cervical cylindromas [1, 2].They are thought to be derived from the multi-potent reserve cells in the transformation zone that can differentiate into both glandular and squamous epithelium [4, 6].

Clinical Presentation

Cervical ACC is generally seen in the postmenopausal age group [4]. A few cases have been reported in women under 40 years of age and are relatively rare in the Asian ethnicity [3, 7]. Clinically, they present with vaginal bleeding and ulcerated hard palpable mass [3]. In this case, ACC presented in a 41-year-old female as a friable cervical growth. The occurrence of this neoplasm in the perimenopausal age group makes this case rare. A review of clinico-pathologic features of recently reported ACC cases has been presented in Table 1.

Pathology

Pathologic features of cervical ACC are similar to ACC in other parts of the body [3]. Similar to salivary ACC, lymphovascular invasion and perineural invasion are also seen in cervical ACC [4, 8]. A point of dissimilarity between cervical ACC and ACC of other sites is the relative paucity of myoepithelial cells in cervical ACC [3]. ACC is a biphasic neoplasm composed of luminal epithelial cells forming tubules containing mucinous matrix and myoepithelial cells forming pseudo lumina containing eosinophilic hyaline material. The tumor shows tubular, solid, and cribriform architecture [3, 8]. The hyaline stroma is positive for periodic acid-Schiff reaction suggesting basement membrane like material [4]. ACC has to be differentiated from other neoplasms with similar morphology such as adenoid basal carcinoma (ABC), basaloid squamous cell carcinoma, mesonephric adenocarcinoma, neuroendocrine tumor, and endocervical adenocarcinoma. This distinction can be made based on immunohistochemistry. The luminal epithelial cells of ACC show positive immunostaining for CD117, and CK7 while the abluminal myoepithelial cells show positive immunostaining for p63, Smooth muscle actin (SMA), Calponin, and S100 [6]. The closest differential of ACC is ABC, characterized by nests of uniform basaloid cells that penetrate the cervical stroma without accompanying stromal reaction. There is an absence of the MYB translocation and shows negativity for CD117 [3, 6]. They are relatively indolent neoplasms with low potential for metastasis and recurrence [4]. Basaloid squamous cell carcinoma (SCC) poses a diagnostic dilemma for ACC with a predominant solid pattern. SCC shows strong positivity with p63 and CK5/6 while it is negative for CK7 and CD117 [3]. Mesonephric adenocarcinomas show various histological patterns, such as tubular, reticular, papillary, and glandular. It presents with florid mesonephric hyperplasia and shows eosinophilic luminal secretion. It can be confused with ACC with a predominant tubular pattern. Mesonephric adenocarcinoma shows positivity for CD10, CK7, CAM5.2, EMA, and calretinin while they are negative for CD117 [9, 10]. Other differentials that need exclusion include Neuroendocrine neoplasm and cervical adenocarcinoma [11, 12]. The immunohistochemical differences have been tabulated in Table 2.

Cervical ACC has been associated with dysplasia and co-existing squamous cell carcinoma reflecting a common cell of origin or a common causative agent for the two lesions [3]. Only a few studies have explored the association of HPV with cervical ACC [6, 13]. The integration of high risk HPV in SCC and ACC has been demonstrated by Shi et al. indicating that HPV might play a significant role in tumor pathogenesis [6]. The surrogate marker for HPV infection, i.e. p16 immunohistochemistry can be employed [6]. However, a few other studies showed that pure ACC of cervical and vulvar origin is unrelated to high-risk HPV, and display non-diffuse, variable expression of p16 [13]. Due to these conflicting results, the association of HPV in the pathogenesis of ACC remains a topic of potential future research. A few studies have shown chromosomal alterations in gynecological ACC such as complex chromosomal changes in chromosomes 1, 4, 6, 11, 14, 22 and recurrent translocation t(6;9)(q22–254;p23–24) leading to a novel oncogenic fusion protein MYB-NFIB, which contributes to MYB overexpression [13].

Treatment and Prognosis

It is important to recognize cervical ACC as it is a rare neoplasm with a worse prognosis when compared to SCC [2]. It is an aggressive neoplasm with the capability to show early metastasis to loco-regional lymph nodes and distant organs, such as lungs, abdominal cavity, and brain [4]. Treatment of cervical ACC follows well-established protocols for cervical carcinomas [7]. It includes surgical resection, radiotherapy, or chemotherapy, either alone or in combination of the above depending upon the clinical stage. Currently, surgical resection remains the mainstay in cervical ACC [7]. There is conflicting data on the importance of adjuvant treatment following radical surgical resection [6]. Patients presenting in the early stages and treated with adjuvant radiotherapy have shown better results than the cases where surgery was the only treatment modality [3]. Chemotherapy plays little role in the treatment of ACC but has been used for recurrent, metastatic, and advanced disease without much success [8]. Tumor features such as large tumor size, deeper stromal invasion, and the presence of lymphovascular emboli are associated with higher recurrence rates and mortality in stage Ib. Advanced cases (stage III and IV) invariably show

Table 1 A review of clinico-pathological features of ACC cases

Author	Age (years)	Clinical presentation	Macroscopic tumor appearance	Microscopic diagnosis	Immunohistochemistry	Treatment given	Follow up (months)	Recurrence
Koyfman et al. [14]	38	Post-coital bleeding	Ulcerated growth	ACC	–	Surgery followed by radiation therapy	11	No
Nishida et al. [15]	78	Vaginal bleeding	Cauliflower-like growth	ACC	Positive for CK17, CK19, pancytokeratin, and 34βE12, Negative for CK14, smooth muscle actin (SMA), or S-100	Radiotherapy	60	No
Seth et al. [16]	34	Vaginal bleeding	Exophytic friable growth	ACC with foci of SCC	Positive for SMA	Surgery	–	–
Elhassani et al. [17]	68	Spontaneous vaginal bleeding	Exophytic ulcerated growth	ACC	–	Concurrent chemo-radiotherapy	12	No
Mohamed Sinaa et al. [18]	36 and 41	Vaginal bleeding and lumbar pain	Mass	ACC	–	radiotherapy followed by surgery	9	No
Nayak et al. [4]	68	Abdominal distension, breathlessness and blood-tinged vaginal discharge	Grayish-white growth	ACC	Positive for SMA and S-100	Surgery followed by concurrent chemotherapy and radiotherapy	6	–
Khadija Benhayoune et al. [19]	80 and 80	Postmenopausal bleeding and hydrorrhea, vaginal bleeding with pelvic pain	Ulcerative, exophytic and friable mass	ACC	Positive for CD117, hormone receptors and focally CK5/6, S-100 protein and CD56	Not available	–	–
Shi et al. [6]	64, 77 and 63	Bloody or watery vaginal discharge	Friable mass	ACC with SCC	ACC: Positive for CK7 and CD117 and patchy p63 SCC: Strong and diffuse p63	Surgery	21.6	No
C. Ribeiro et al. [8]	82	Postmenopausal bleeding, inappetence, and weight loss	Vegetative and friable lesion	ACC	Positive for CAM 5.2 and collagen IV	Surgery followed by radiotherapy and chemotherapy	24	No
Song et al. [20]	76	Vaginal bleeding	Polypoid mass	ACC with SCC	ACC: Positive for CD117, S-100 protein, p16 and focal p63 SCC: Diffusely positive for p63 Negative for CD117 and S-100	Surgery followed by concurrent chemo-radiotherapy	14	Yes

Table 2 Differential diagnoses of ACC with their Immunohistochemical profile

Pathology	Immunohistochemistry															MYB translocation
	CK7	CD117	P63	SMA	Calponin	S100	CK5/6	CK14	Synaptophysin	Chromogranin	CD56	CD10	CAM 5.2	PAX8	Calretinin	
ACC	+	+	+ in myoepithelial cells	+	+	+	−	−	−	−	−	−	−	−	+	
ABC	−	−	+	−	−	−	+	+	−	−	−	−	−	−	−	−
Basaloid SCC	−	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−
Mesonephric adenocarcinoma	+	−	−	−	−	−	−	−	−	−	−	+	+	+	+	−
Neuroendocrine neoplasm	−	−	−	−	−	−	−	−	+	+	+	−	−	−	−	−
Endocervical adenocarcinoma	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

poor outcome [3]. The solid ACC has a worse outcome followed by cribriform and tubular subtypes [3].

Conclusion

ACC is an aggressive cervical cancer with a higher incidence of distant metastasis and local recurrence. A correct diagnosis of ACC should be made distinguishing it from other tumors showing similar histologic features. Treatment regimens should be enhanced and a careful follow-up of such cases is recommended. An in-depth study of this rare tumor should be encouraged to understand the histogenesis and role of HPV in cervical ACC.

Funding No funding obtained

Declarations

Conflict of interest No conflict of interest to disclose.

Ethical approval All individuals listed as co-authors of the manuscript qualify for every one of the four criteria listed in the ICMJE recommendation for qualification of authorship.

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