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Case Report

Glassy cell variant of human papillomavirus associated poorly differentiated adenosquamous carcinoma with concurrent adenocarcinoma in situ: a rare case report

Sonal Raut*

Department of Histopathology, Manipal TRUtest Laboratory, Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Sonal Raut,
E-mail: sonalghavghave@gmail.com

ABSTRACT

Glassy cell carcinoma (GCC) of the uterine cervix is a rare neoplasm, first described by Gluksman and Cherry in 1956. It is a poorly differentiated adenosquamous carcinoma, comprising about 1-2% of all cervical cancers. It is considered to originate from the subcylindrical reserve cells of the cervix and has been associated with human papillomavirus (HPV). Histologically glassy cell carcinoma is composed of nests of large cells with ground glass nucleoli. Nuclear pleomorphism and tumour giant cells are frequently seen. Mitotic activity is brisk. Infiltration by eosinophils and plasma cells with admixture of lymphocytes is a characteristic feature. we report a case of 44-year female who presented with per vaginal bleeding and white discharge which was diagnosed clinically as cervicitis. On pap smear it was reported as NILM- inflammation probably because of its rich inflammatory stroma. Ultrasonography (USG) abdomen and pelvis done which showed mild bulky cervix with changes of cervicitis. We performed P16 which was diffuse block like positivity along with p63 and CK 7 which confirms the adenosquamous presentation and highlights adenocarcinoma in situ arising from endocervical glands. Cervical GCC was recognized as a rare histological entity associated with poor prognosis since the report from Cherry and Glucksmann. We reported a rare case of GCC of cervix variant of poorly differentiated adenosquamous carcinoma associated with HPV and concurrent adenocarcinoma in situ, confirmed on immunohistochemistry.

Keywords: Glassy cell carcinoma, Cervicitis

INTRODUCTION

Glassy cell carcinoma (GCC) of cervix is a rare subtype of adeno-squamous cell carcinoma (ASC), which was reported by Cherry and Glucksmann first as an aggressive subtype of cervical carcinoma with poor prognosis.[1] It accounts for 0.2% to 9.3% of all cervical cancers, and 2% to 30.2% of cervical adenocarcinomas.[2-4]

We present a case of GCC of cervix, a variant of poorly differentiated adenosquamous carcinoma which is also human papillomavirus (HPV) associated which was proved by p16 immunohistochemistry. It also showed concurrent adenocarcinoma in situ. It was clinically and on radiology detected as cervicitis.

CASE REPORT

A 44-year-old female presented to local hospital out-patient department (OPD) with the complaint of per vaginal bleeding and discharge for approximately one month. She was perimenopausal and had irregular menses. Per speculum examination showed congested cervix with erosion. Per vaginal examination showed inflamed cervix. Ultrasonography (USG) showed mild bulky and hyperreflective cervix. Cervical pap smear cytology sent which depicted as chronic cervicitis. Total abdominal

hysterectomy with bilateral salphingo-opherectomy was done.

Histopathological examination was done. Grossly, uterus was only minimally enlarged. cervix showed an infiltrative irregular friable tan grey mass involving ectocervix circumferentially, measuring 2.5×2×1.5 is seen extending into the endocervical canal however lower uterine segment was free of tumor grossly (Figure 1).

Figure 1: Specimen of uterus with cervix showing friable tan grey brown endophytic mass involving ecto and endocervix.

Tumor is seen reaching upto the inked adventitial/ horizontal margin which was more than half of the thickness of cervical stroma. Parametrial tissue, vaginal margins and pelvic lymph nodes were not received with the specimen probably considering the clinical diagnosis of cervicitis. Microscopically, cervical tissue showed a tumor arranged in papillae, islands, nests as well as singly infiltrating the cervical stroma with predominantly diffuse eosinophil rich stromal inflammation (Figures 2 and 3).

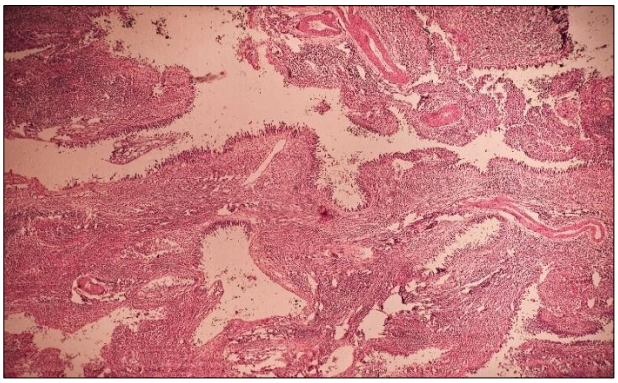

Figure 2: Tumor arranged in papillae, nests, islands and singly infiltrating cells (40x).

The cells are highly pleomorphic, have hyperchromatic nuclei, prominent nucleoli, moderate to abundant eosinophilic granular cytoplasm and well-defined cell membrane. Many bizarre looking sarcomatoid cells and tumor giant cells were present (Figure 5). Brisk mitotic activity (~25 mitotic figures/10 HPF) including atypical mitotic figures seen. foci of adenocarcinoma in situ were also present (Figures 4 and 6). Ectocervical and circumferential margin was involved by tumor.

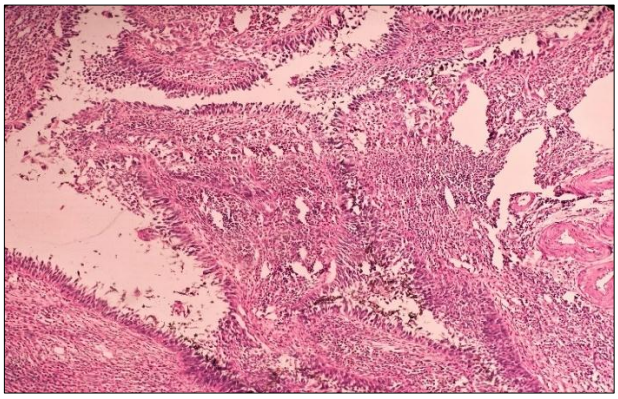

Figure 3: Highly pleomorphic, hyperchromatic tumor cells with abundant eosinophilic cytoplasm (100x).

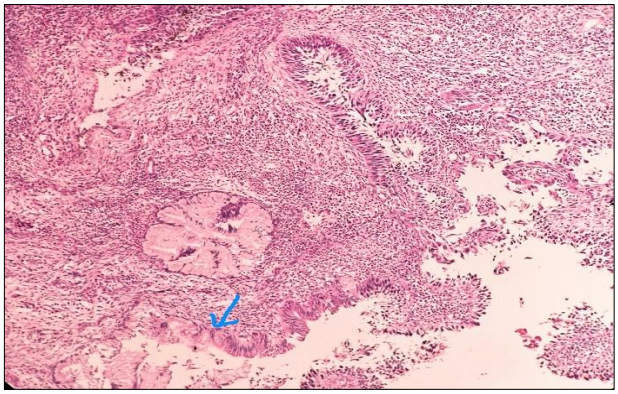

Figure 4: Carcinoma in situ arising from endocervical glands (blue arrow) (100x).

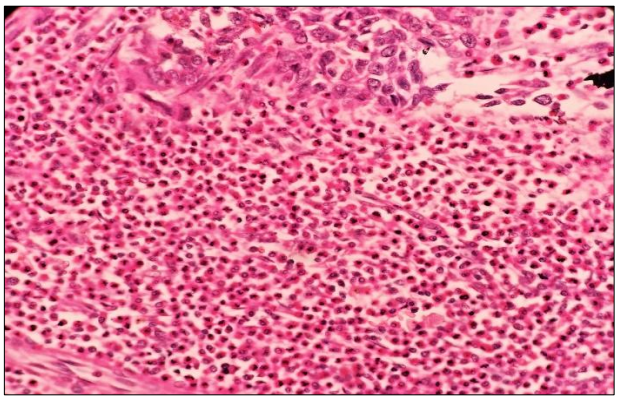

Figure 5: Eosinophil rich stroma with tumor giant cells (400x).

Slides stained with Periodic acid schiff's (PAS) stain was seen positive in cytoplasm focally. Immunohistochemistry for P16 was performed and it was diffuse strong block positive in tumor cells involving ectocervix, endocervix as well as in situ component (Figures 7 and 8).

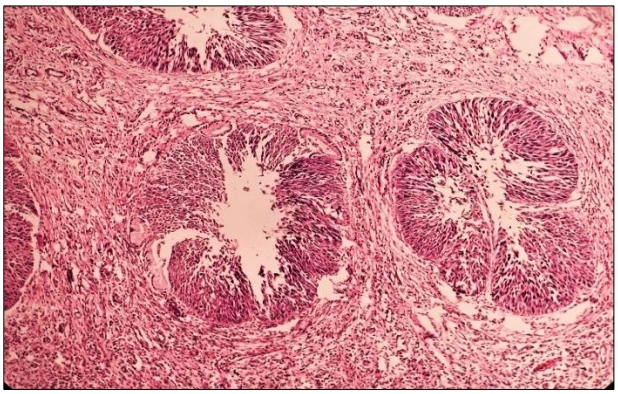

Figure 6: Islands of Adenocarcinoma in situ (100x).

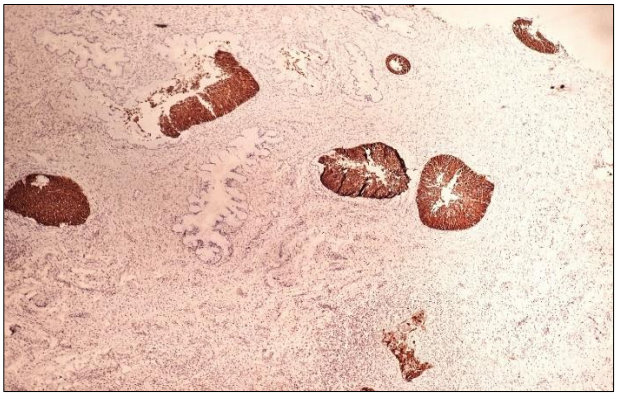

Figure 7: P16 block positivity in tumor and in situ component (40x).

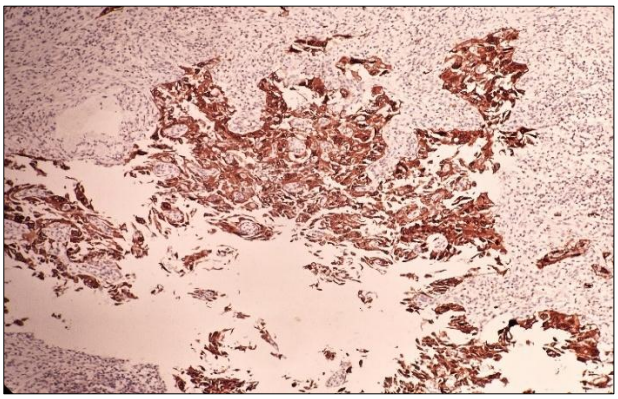

Figure 8: P16 block positivity in invasive tumor cells (100x).

P63 and CK 7 immunostain performed which demonstrated adenosquamous differentiation of tumor cells. In situ adenocarcinoma component was highlighted by CK 7 stain which was negative for P63 (Figures 9 and 10). Depending upon the histopathological characteristics and IHC findings, diagnosis of glassy cell variant of poorly differentiated adenosquamous carcinoma, HPV associated (usual type and Silva system pattern C) with concurrent adenocarcinoma in situ component.

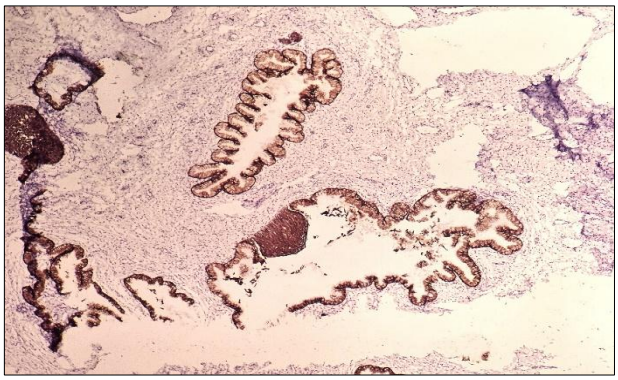

Figure 9: CK7 strong membranous staining highlighting the adenocarcinoma in situ (100x).

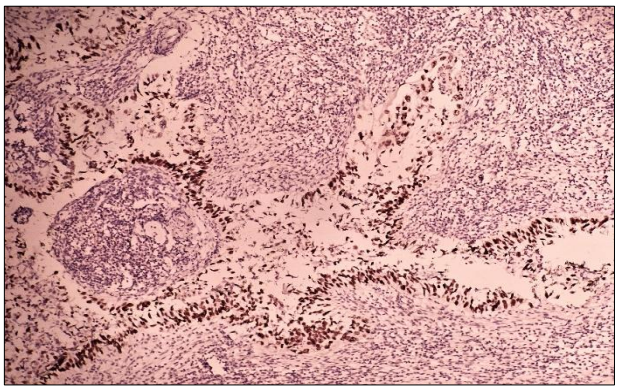

Figure 10: P63 strong nuclear staining in tumor cells (400x).

DISCUSSION

Cervical GCC was recognized as a rare histological entity associated with poor prognosis since the report from Cherry and Glucksmann.[1] 2020 World Health Organisation (WHO) classification of cervical Adenocarcinoma is based on division of HPV associated and HPV independent status of tumors. Glassy cell carcinoma which is variant of poorly differentiated adenosquamous carcinoma of cervix is HPV associated which is demonstrated by P16 immunostaining. HPV analysis is not necessary for the diagnosis. If "block-type" reactivity is detected immunohistochemical P16 expression is considered to be a surrogate marker for HPV association. HPV-associated Adenocarcinoma of the cervix uteri is determined using the prognostically relevant Silva pattern.[5] Wang et al observed in their study, the median age of 20 GCC patients was 46 years (range from 33 years to 69 years) which is three years younger than that of common subtype of cervical carcinoma. Clinical symptoms were that of per vaginal bleeding and discharge. 6 our case was of 44-year female presented with same complaints. Her pap smear depicted as cervicitis.

Glassy cell carcinoma grossly shows an exophytic growth. Endophytic tumors are found less frequently. It has a rapid growth pattern with metastases into lymph nodes and

distant organs.[7] In our case, grossly tumor was endophytic and infiltrating diffusely into the stroma involving endocervix and engulfing ectocervix. Horizontally also it involves the surgical margin.

Habara et al observed Inflammatory cell infiltration predominantly of plasma cells in their case.[8] our case predominantly showed diffuse sheets of tumor infiltrating eosinophils only which is the characteristic and typical microscopic feature of this entity.

The main characteristic cytological findings of poorly differentiated adenosquamous carcinoma (glassy cell carcinoma) are as follows: cell clusters are characterized by a syncytial or sheet-like arrangement of cells; the cytoplasm has a moderate volume and is pale and coarsely granular, i.e., with a "ground glass" appearance; the nuclei are large and round with homogeneous fine-granular chromatin; and a single large nucleolus and multiple small nucleoli are prominent.[4] Our case showed sheets of infiltrative cells with pleomorphic nuclei, prominent nucleoli, abundant eosinophilic granular (glassy) cytoplasm and tumor giant cells with brisk mitosis.

Cervical GCC patients who had at least one high or intermediate risk factor should receive adjuvant treatment. High risk factors include: large lesion; metastases to lymph nodes; involvement of parametrium; and insufficient surgical margin.[9] Intermediate risk factors include: lympho-vascular space invasion; deep stromal invasion; and tumor size >3 cm^2.

Our case falls under the high-risk group as it has insufficient surgical margin and deep stromal invasion so requiring adjuvant therapy. Parametrium and lymph node status could not be assessed. Our case belonged to FIGO stage IB2.

Wang et al, in their series, studied the HPV prevalence was 44.4% which was a bit higher than that of previous study (34.8%).6 Our case too showed strong diffuse block positivity on immunohistochemistry for P16 which is a surrogate marker for HPV.

It is important to differentiate it from squamous cell carcinoma and adenocarcinoma as the GCC carries much poorer prognosis and high rate of metastasis outside pelvis.[10] Immunohistochemistry will help to differentiate between the two and subsequently help to confirm this rare entity with poor prognosis so that patient can get adjuvant therapy.

Relative early age of presentation with associated typical histologic features of rich eosinophilic stroma and poorly differentiated cells with glassy cytoplasm and well-defined border will be the clue for diagnosis. Our case additionally showed well defined adenocarcinoma in situ component.

The limitations of our study were that as it was misdiagnosed as cervicitis clinically, incomplete surgery was performed without lymph nodes, vaginal vault or parametrium which leads to incomplete staging and subsequent treatment which could be fatal to the survival of the patient. Follow up of the case could not be done.

CONCLUSION

We reported a rare case of glassy cell carcinoma of cervix variant of poorly differentiated adenosquamous carcinoma associated with HPV and concurrent adenocarcinoma in situ. It is essential to identify, diagnose and report this rare entity from its characteristic histopathological features so that patient gets an early and prompt treatment as it has fatal outcome. As it affects perimenopausal women and associated with HPV, screening for the same can be preventive and lifesaving.

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