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Glassy cell carcinoma of cervix-A chance diagnosis from pap smear with immunohistochemical confirmation

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ABSTRACT

Glassy Cell Carcinoma is a rare malignancy of uterine cervix with aggressive biological behaviour and poor prognosis. Patients usually present with abnormal bleeding or discharge per vaginum of a short duration. It affects comparatively young women of 3rd to 4th decades than other invasive carcinomas of cervix. Histologically it is diagnosed by sheets of large polygonal cells with distinct cell borders, finely granular ground glass like cytoplasm and vesicular nuclei with prominent nucleoli. This is a rare subtype of poorly differentiated adenosquamous carcinoma and proved immune histochemically by positivity to CEA, CK7and Pan CK with HMWK. But cytologic diagnosis from pap smear can be difficult and can be established by detection of large round to polygonal cells with finely granular cytoplasm and prominent nucleoli. Finding of an inflammatory background is a helpful adjunt to a correct diagnosis. Since the present case was a young patient, surgery followed by chemotherapy was given with a good response. Although rare, such tumours should be kept in mind while dealing with younger patients of suspected carcinoma of cervix. We present a case of glassy cell carcinoma of cervix in a 30 year old female diagnosed in pap smear with clue to cytologic interpretation.

INTRODUCTION

Glassy cell carcinoma (GCC) of cervix is a rare subtype of poorly differentiated adenosquamous carcinoma acounting for less than 1% of all cervical cancers. [1,2]. Patients are usually younger, compared to the invasive cervical carcinomas and belong to 3rd to 4th decades of life. [3]It has a rapid growth and within a short period presents as a large bulky exophytic mass. It is named as glassy cell carcinoma due to presence of glassy cells. Glassy cells are characterised microscopically by large polygonal cells with abundant granular cytoplasm with prominent nucleoli.(Glassy cells)Clinical course of these tumours is aggressive with a tendency for early metastasis.

Diagnosis of rare entities like this in the Pap test, pose challenges due to the infrequent occurrence in the daily practice of cytology. Furthermore, these conditions give rise to important diagnostic pitfalls to be aware of in the Pap test. Recognition of GCC can help to improve the accuracy and precision of Pap test diagnoses and decrease the potential for misdiagnosis and litigation. Also, it will help achieve more timely management of patients with such conditions. Therefore, we present the cytologic findings in a case of GCC in a 30 year old patient with clue to correct interpretation.

CASE REPORT

A 30 year old female attended the Gynaecological OPD, with the complaints of intermittent bleeding P/V for last 3 months. On examination patient was of average body built except mild pallor. Systemic examination did not reveal any abnormalities. Routine investigations revealed haemoglobin-9.8gm%, DC-N- 68, E-03, B-00, L-28, and M-01. TLC-6,800/mm^3 of blood. Peripheral smear revealed mild hypochromic microcytic anaemia. Per speculum examination showed an exophytic cervical mass of size about 5x4x3cm with obliterated fornices. In per vaginal examination, uterus was bulky and bilateral parametrium were thickened. USG of abdomen and pelvis showed an irregular mass of size 49.8mmx36.7mmx28.5mm in cervical area. Pap smears were taken and showed clusters of large pleomorphic cells with abundant eosinophilic cytoplasm, hyperchromatic nuclei and prominent nucleoli. (Fig.1A&B) Dyskeratotic cells were absent. A prominent inflammatory background was detected. Biopsy was advised and grossly multiple bits of grey-white tissue were received. Microscopy revealed nests of polygonal cells with abundant granular eosinophilic to clear cytoplasm, vesicular nuclei and prominent nucleoli separated by fibrous stroma. Heavy inflammatory cell infiltration rich in eosinophils were present both in the centre of cell clusters and also in the fibrous stroma.

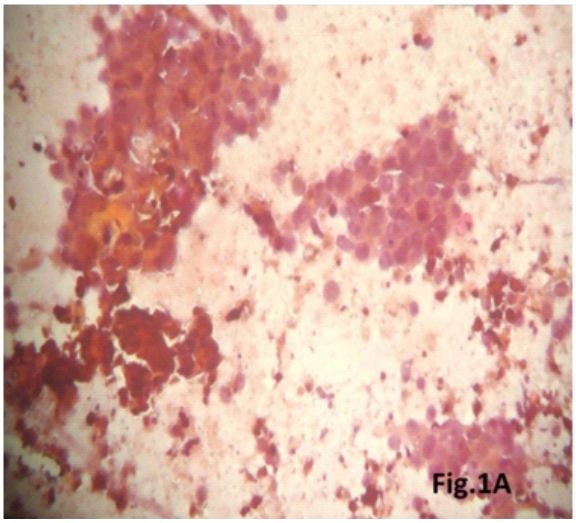

Fig.1A - Cytologic features of GCC, Pap stainx40

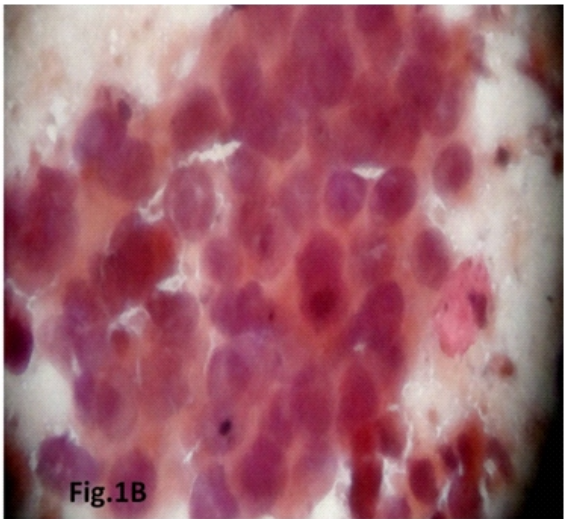

Fig. 1B - Clusters of large cells with abundant eosinophilic cytoplasm, hyperchromatic nuclei & prominent nucleoli. Pap stainx400

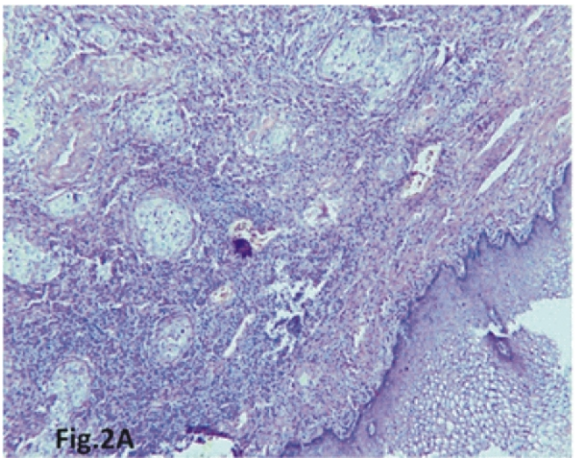

Fig.2A - Syncitial clusters of malignant cells over inflammatory background. H&E stainx40

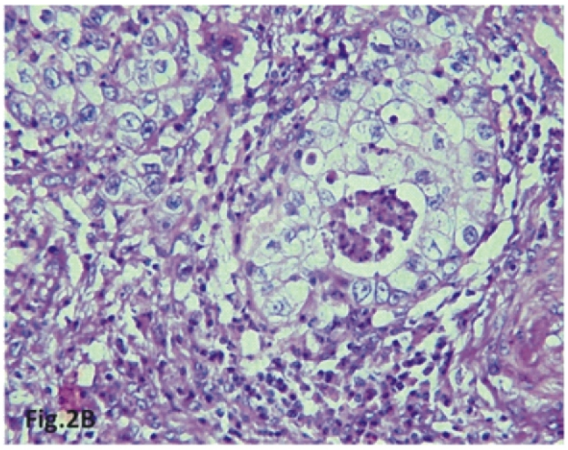

Fig. 2B - Cluster of glassy cells with eosinophils in center .H&E stainx400

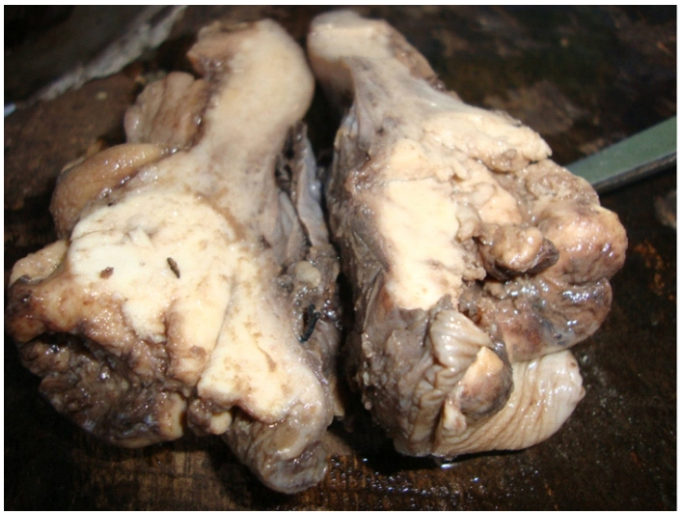

Fig.3 - Gross photograph showing bulky friable growth in cervix.

High mitotic activity and many apoptotic cells were also detected. (Fig.2A&B). The patient was planned for total hysterectomy with pelvic lymphadenectomy and the gross specimen included uterus and cervix with pelvic lymph nodes. There was a fungating friable growth of 5x4x3cm involving ecto and endocervix and was extending to lower uterine segment. (Fig.3) Sections were taken from growth, uterine wall, parametrium, vaginal flap and all the lymphnodes. The mass was confined to cervix but 4/10 lymphnodes showed metastatic deposits. The uterine wall, vaginal flap, and parametrium were not involved. The HP sections were subjected to immunostains and the tumour cells were positive for CEA, CK7 and HMWK and negative for CK20.(Fig.4 A,B,C,D) So a final diagnosis of glassy cell carcinoma of cervix of FIGO-stage pTIB2pN1pMX was rendered.

DISCUSSION

Glassy cell carcinoma is a rare aggressive malignant tumour of uterine cervix characterized by distinctive cytologic and histologic features. The entity is defined by presence of classic

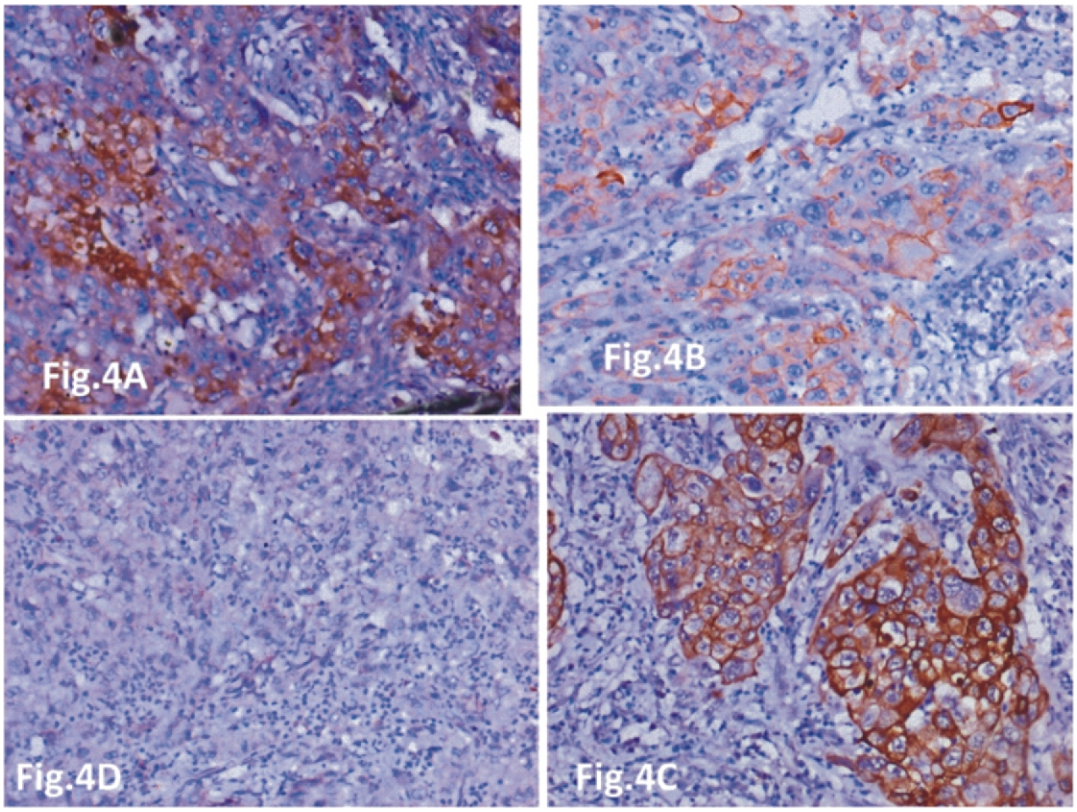

Fig.4 - IHC of tumour cells A-CEA,B-HMWK, C-CK7 D-CK20

glassy cells in clusters separated by fibrous stroma with dense inflammation rich in eosinophils.[4] The presence of abundant pale eosinophilic granular cytoplasm in round to polygonal cells with low nuclear cytoplasmic ratio is the signature of glassy cell carcinoma. The membrane stains positive with PAS stain which stains bright pink. Features like intercellular bridges, dyskeratosis and intracellular glycogen may be lacking in many tumour cells. But , focal abortive keratin production, squamous or glandular differentiation and clear cell change may be detected in some cases. Percentage of glassy cells required for diagnosis is not clearly stated, but many propose for a minimum of 30% of cells with glassy appearance in a tumour to make a diagnosis of glassy cell carcinoma.[3]

Even though it is most commonly encountered in the cervix, can rarely be seen in endometrium, vagina, urethra, fallopian tube and colon. [5]Patients are approximately 10 years younger than those with other invasive carcinomas of cervix. Some of them may present with associated pregnancy also. Glassy cell carcinoma is considered as a rare variant of adenosquamous carcinoma of cervix and is positive to both glandular (CEA, CAM5.2, MUC1, MUC2) and squamous (p63, CK34BE12, HMWK) markers in immunohistochemistry. These tumours show a very high proliferative index > 70%. [6]Deoxyribonucleic acid (DNA) of HPV types 18 and 16 have been detected in the tumour cells of glassy cell carcinoma.[7] GCCs may originate from multipotential stem or reserve cells that undergo early squamous differentiation. The presence of HPV 18 might stimulate biphasic squamous and glandular differentiation.[8]

Cytology smears of GCC show syncitial clusters, small nests and scattered large malignant cells over a background of necrotic debris, proteinaceous material and abundant inflammatory exudate chiefly eosinophils or lymphocytes. [9,10]The cells have a moderate amount of finely granular cytoplasm, distinct cell membranes, large nuclei and prominent single or multiple nucleoli. In cervical cytologic smears, GCC has to be distinguished from atypical reparative cells, large cell non-keratinizing carcinoma, clear cell carcinoma (mesonephroid carcinoma) and the rare lymphoepithelioma-like carcinoma of the cervix.[9] Atypical reparative cells may be large, pleomorphic with large nuclei but the classic glassy cells and the typical inflammatory background are not evident. Non-keratinizing SCC shows a greater degree of squamous differentiation, intercellular bridges, coarse chromatin and intracellular glycogen. It can be ruled out due to absence of ground glass cytoplasm, well defined cell borders, prominent nucleoli and the prominent eosinophilic infiltrate seen in GCC. Occasionally, large areas of clear cell differentiation are seen in GCC. These cases may be confused with clear cell carcinoma. But, in clear cell carcinoma the cells are smaller, arranged in acinar or papillary pattern with characteristic hobnail cells with the nuclei protruding away from the base of the cell. GCC may be difficult to distinguish from lymphoepithelioma like carcinoma of cervix which shows large, uniform tumour cells with often oval, vesicular nuclei in an inflammatory background rich in lymphocytes. Also, these cells lack the glassy cell features .[11]The diagnosis in the above patient was made by the finding of characteristic cytologic features which were later confirmed by histology and immunohistochemistry.

In Haematoxylin and eosin stained sections in low power GCC gives a very characteristic picture with pale staining cell nests and darker stroma with inflammatory cells. Cell nests comprise of the typical glassy cells. Eosinophils are present in stroma and also seen infiltrating into the centre of tumour islands.Differential diagnosis in histology includes poorly differentiated neoplasms involving cervix like large cells

nonkeratinizing squamous cell carcinoma, poorly differentiated adenocarcinoma, clear cell carcinoma and clear cell sarcoma (Alveolar soft part sarcoma of female genital tract). But GCC exhibits only focal squamous or adenocarcinomatous differentiation, and have extensive eosinophilic infiltrate, which is characteristic. Clear cell carcinoma contain abundant intracytoplasmic glycogen in contrast to the relative absence of it in GCC. Also alveolar soft part sarcoma is differentiated by an alveolar pattern and PAS+ve crystals in the cytoplasm.

Due to its rapid growth usually patients present in an advanced stage and with a bulky exophytic growth and with a tendency for pelvic and extrapelvic metastasis. Local recurrence occurs frequently and encountered in vaginal vault, parametrium, ovaries and paraaortic lymph nodes. Risk factors for recurrence are lymphatic invasion, deep stromal invasion of size more than 3cm/.[4]IHC study shows positively for ER, PR, Her2/neu, Her2-neu overexpression correlates with aggressive behaviour and worse clinical outcome.

The 5 year survival is approximately 13 to 30%. The biological behaviour is similar to other poorly differentiated carcinomas, but these tumours peculiarly affects younger patients, there by making early recognition extremely important. All the 3 modalities of treatment like surgery, radiotherapy and chemotherapy are tried, showing varied results.However, patient shows significant improvement with combined radical surgery, aggressive radiation therapy and Cis platin containing chemotherapy.[4]The above patient did not undergo bilateral salpingo-oophorectomy because of her younger age. She was given 6 cycles of chemotherapy and responded well.

CONCLUSION

Recently, GCC of cervix appears to have a better prognosis than previously reported. Patients with lymphovascular invasion, deep stromal invasion, large tumour size are at highest risk for pelvic relapse. Because of its worse prognosis, early diagnosis from a screening method like pap smear testing carries utmost significance and we have tried to provide the important diagnostic clues for the correct interpretation.

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