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Case Report

Newly recognized face of cervical cancer: Gastric type of Mucinous adenocarcinoma- A case report and brief literature review

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ABSTRACT

Gastric type mucinous adenocarcinoma (GAS) is a mucinous type of endocervical adenocarcinoma described in WHO 2014. It is known for its aggressive nature, recurrence rate, distant metastasis and poor response to therapy. It is associated with minimal deviation adenocarcinoma (MDA) which belongs to the same spectrum of the disease. Hence it is very important to diagnose these rare tumors and differentiate it from usual endocervical and metastatic adenocarcinomas. We describe a case of Gastric type of mucinous adenocarcinoma, which is MUC6, mCEA positive and p16 negative.

1. Introduction

Endocervical adenocarcinomas are most common cervical adenocarcinomas.[1,2] The other subtypes include mucinous carcinoma, villoglandular carcinoma, endometroid carcinoma, clear cell, serous and mesonephric type.[3] Gastric type mucinous adenocarcinoma is nonHPV related tumor, a subtype of mucinous adenocarcinoma. GAS show distinct morphological and immunophenotype profile and is associated with Minimal deviation adenocarcinoma. Immunoprofile is similar to any gastric phenotype morphology and express MUC6 and HK1083 and immunonegative for p16 and PAX8. The tumor is chemoresistant and shows aggressive behavior in its early stage too. Five year disease free survival rate in GAS is 38% compared with usual type adenocarcinoma74%.[4]

2. Case Report

We are reporting a case of 67 year lady who presented with lower abdominal pain, she underwent pap smear examination elsewhere and was reported as negative for atypical cells. Abdominal ultrasound report showed bulky uterus with pyometra and cervical stenosis.

Received uterus with cervix and bilateral adnexa, grossly no visible growth was appreciated, however cervix showed mild erosion and firm areas. Endometrial cavity was dilated, bilateral ovaries and fallopian tubes were grossly unremarkable. Microscopically cervix showed irregularly dilated endocervical glands infiltrating deep into the cervical stroma and these atypical glands were surrounded by desmoplastic stroma, they were bland looking and lined by mucin filled tall columnar cells and admixed with morphologically different looking nests of tumor cells exhibiting large pale to clear cytoplasm, irregular hyperchromatic nuclei with distinct cell borders (Figures 1 and 2). Lymphovascular emboli and perineural invasion was noted. Tumor cells are reaching the deep cervical stroma and 1mm away from the inked serosal margin. Entirely submitted ovaries and fallopian tubes were free of tumor deposits. Based on the morphology, diagnosis of adenocarcinoma was made and immunohistochemistry was suggested to establish the diagnosis and to rule out metastasis.

Special stain AB PAS, highlights the neutral mucin in atypical glands and tumor nests (Figure 3). Tumor cells showed strong positivity for CK7, mCEA, MUC6 and was

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negative for CK20, P16, ER, TTF1, PAX8. (Figures 4, 5 and 6).

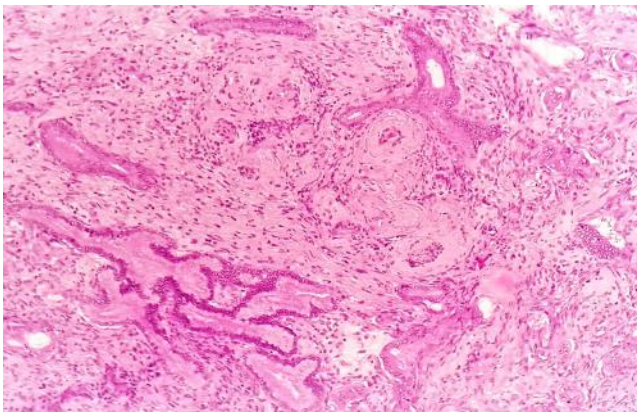

Fig. 1: Low magnification (10X) H and E stain showing irregular dilated claw shaped endocervical infiltrating deep into the cervical stroma

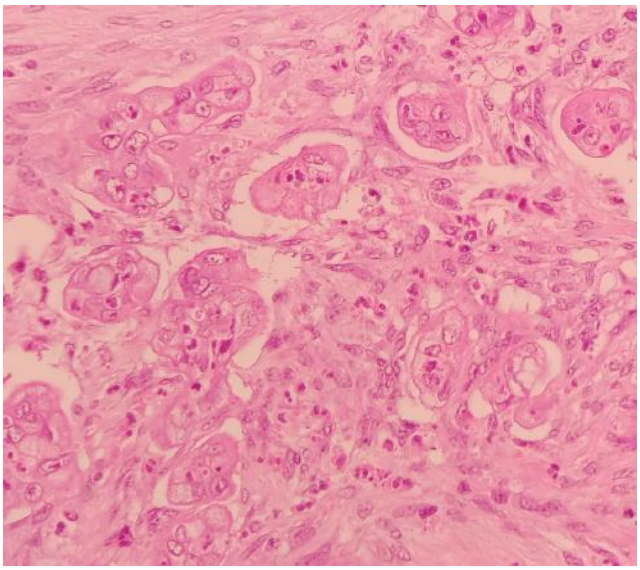

Fig. 2: 40 X magnification H and E stain showing nests of tumor cells with abundant clear to eosinophilic tumor cells with irregular nuclei

3. Discussion

Usual endocervical adenocarcinoma remains the most common type of cervical adenocarcinoma and are HPV associated. There are Non HPV associated tumors which includes, gastric type endocervical adenocarcinoma, clear cell carcinoma and mesonephric type.[1]

Gastric type mucinous endocervical adenocarcinoma and MDA are non-HPV associated adenocarcinomas exhibiting gastric phenotype. It is the second most common subtype of endocervical adenocarcinoma and accounts for 25% of

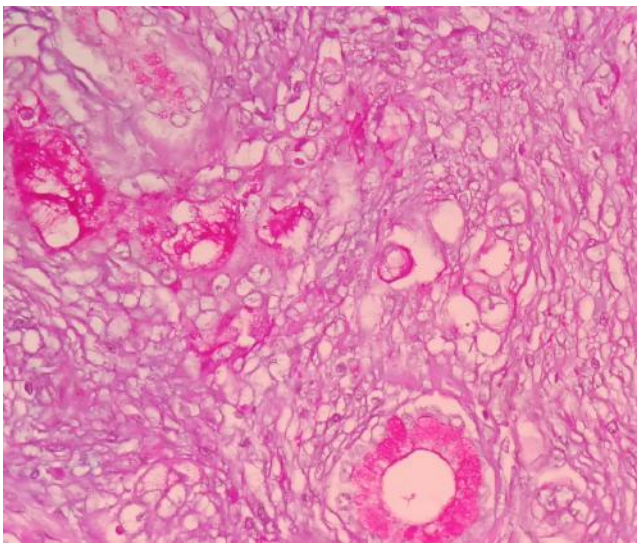

Fig. 3: 40 X AB PAS highlights the neutral mucin

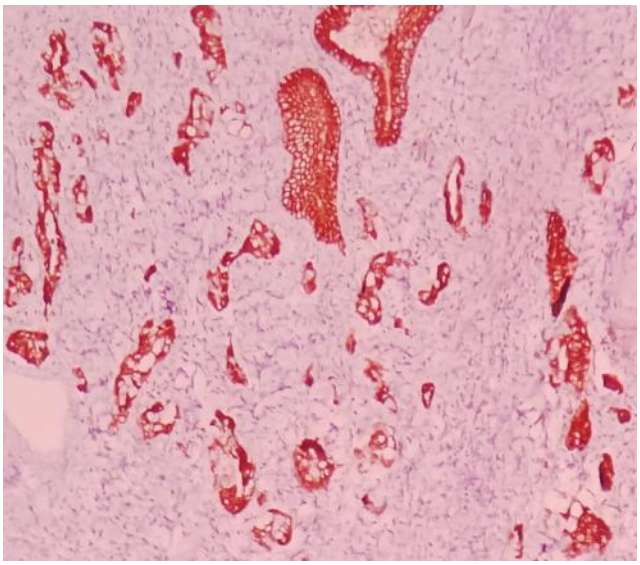

Fig. 4: 40 X Tumor cells show positivity for mCEA

all cervical adenocarcinomas.[2] Kojima et al first described GAS as tumor with voluminous, clear to pale eosinophilic cytoplasm, hyperchromatic irregular nuclei and distinct cell borders. Most of the patients are detected at later stages of the disease.

Minimal deviation adenocarcinoma is well differentiated form of GAS and represents the same spectrum of the disease with two year survival rate of 50% for stage I disease and 20-30% for higher stage disease.[3,5]

Minimal deviation adenocarcinoma or adenoma malignum tumors are histomorhologically bland looking, exhibit irregularly dilated glands lined by mucin filled tall columnar epithelium without nuclear atypia and nil to rare mitotic figures. These glands are surrounded by

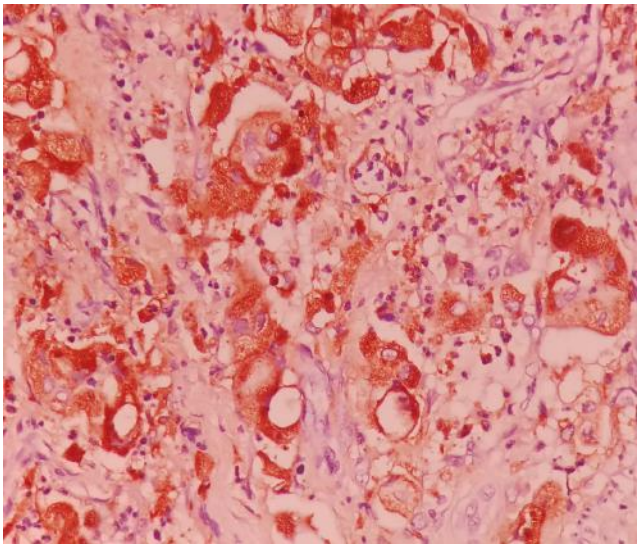

Fig. 5: 40X Tumor cells show diffuse strong MUC6 positivity

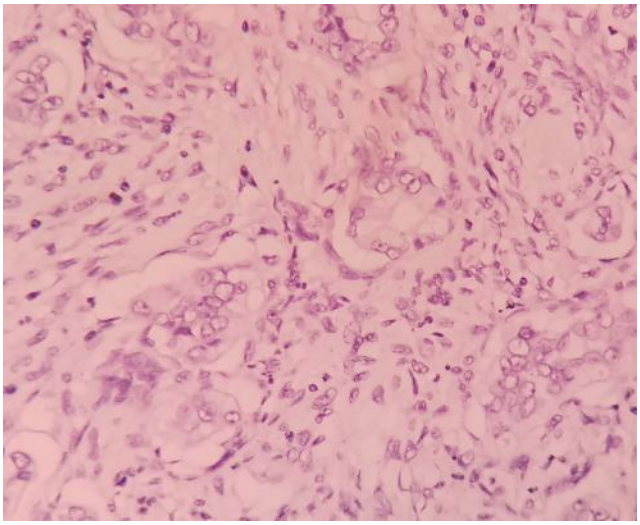

Fig. 6: 40 X Negative p16 immunostain in tumor cells

desmoplastic stroma, show lymphovascular emboli and perineural invasion.[6] Special stain AB PAS highlights the neutral mucin. Because of the bland looking morphology of the cells most of these cancers are missed in routine cervical screening tests. Both MDA and GAS expresses the gastric phenotype and are positive for CK7, mCEA, MUC6 and HK1083. Negative for CK20, P16, ER, TTF1, PAX8. HPV DNA is negative.

Our case was positive for CK7, mCEA and MUC6. Negative for P16, PAX8, CK20, ER, TTF1. HK1083 was not done in our case.

Differential diagnosis of this rare entity includes both benign and malignant lesions. In benign lesions we have to rule out Lobular endocervical glandular hyperplasia (LEGH) and diffuse lobular endocervical glandular hyperplasia, LEGH shows central dilated duct surrounded by multiple small ducts, these glands are benign looking and desmoplastic stroma is not seen surrounding the glands which is seen in GAS and is highlighted by Smooth Muscle Actin(SMA).[7] Rabban et al showed PAX2 positivity in all cases of LEGH and PAX2 negativity in GAS.

Malignant lesions differentials include primary and metastatic tumors. In primary, GAS has to be differentiated from Usual type endocervical adenocarcinoma(UEA). UEA are mucin filled tall columnar cells exhibiting nuclear atypia, mitotic figures, apoptotic debris and express diffuse p16 positivity, in contrast GAS expresses MUC6, HK1083 positivity and is p16 negative. GAS is differentiated from clear cell carcinoma based on the morphology and IHC markers, as clear cell carcinoma show clear cells, tubulocystic and hobnail pattern. Expresses HNF-1beta positivity and is negative for MUC6 and CAIX. Metastatic tumors are differentiated based on the history and imaging findings and tumor markers.

Shanshan Lu et al described extensive spread of the disease involving vagina, corpus, ovaries and fallopian tubes. Fourteen patients died of the disease after two,ten,twenty and twenty four months post surgery.[7]

A very recent study done by Swati Garg et al using next generation sequencing showed P53 as the most common mutation followed by MSH6, CDKN2A/B, POLE etc.[8]

Kojima et al published the cases of UEA and GAS, compared the response rates in stage I and stage II disease, the response rate of stage I of GAS is 46.2% compared to UEA which is 85%. For stage II disease the response rate was 68.8% for UEA and for GAS there is no response at all. Five year progression free survival is 38.5% vs 75% and overall survival rate is 36.6% vs 90.0%.[4]

In the study by Shin Nishioet al, all the cases are significantly associated with bulky mass, higher stage and nodal involvement, they concluded that GAS showed aggressive behavior with ominous histopathological predictors as well as decreased survival rate.[9]

Since our patient was diagnosed correctly at an early stage, there was no recurrence or residual disease after one year post hysterectomy and 6 cycles of chemoradiation.

4. Conclusion

Gastric type of mucinous adenocarcinoma is aggressive chemo-resistant tumor. Morphological suspicion is necessary in these cases. Accurate diagnosis of these lesions is important for aggressive management of the patients.

5. Source of Funding

None.

6. Conflict of Interest

None.

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