OPEN ACCESS

GAVIN PUBLISHERS

Cytology & Histology Reports

Hassan NH, et al. Cytol Histol Rep 2: 110.

DOI: 10.29011/CHR-110.100010

Research Article

Gastric-Type Adenocarcinoma *in-Situ* of the Uterine Cervix: An Emerging Entity

Tay Amos[1], Chun Yuen Chow[1], Gudi Mihir[2*], Yeo Yen Ching2

1Department of Anatomical Pathology, Singapore General Hospital, Singapore

2Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore

[*]**Corresponding author:** Gudi Mihir, Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore. 100 Bukit Timah Rd, Singapore 229899 Tel: +6563945853; Email: gudi.mihir.a@kkh.com.sg

Citation: Amos T, Chow CH, Mihir G, Ching YY (2019) Gastric-Type Adenocarcinoma *In-Situ* of the Uterine Cervix: An Emerging Entity. Cytol Histol Rep 2: 111. DOI: 10.29011/CHR-111.1000011

Received Date: 7 July 2019; **Accepted Date:** 17 July 2019; **Published Date:** 25 July, 2019

Abstract

Gastric-Type Adenocarcinoma (GAS) is a rare and aggressive subtype of endocervical adenocarcinoma. Accumulated evidence suggests that a subset of atypical Lobular Endocervical Glandular Hyperplasia (LEGH) and Gastric Type Adenocarcinoma *in Situ* (GAIS) may be associated with and represent precursors of GAS. GAIS is rare and not yet well characterised. Herein, we summarise the current available literature on histological and cytological features of GAIS. GAS and GAIS are likely to increase in relative importance in the era of HPV vaccination and HPV testing, yet will prove a diagnostic challenge due to lack of familiarity, subtle histologic and cytologic features and lack of association with HPV.

Keywords: Adenocarcinoma *in-situ*; Cervix; Gastric-type

Abbreviations: Gastric-type adenocarcinoma - GAS; Minimal deviation adenocarcinoma - MDA; Gastric-Type Adenocarcinoma *In-Situ* – GAIS; Human papilloma virus - HPV; Lobular Endocervical Glandular Hyperplasia - LEGH; Adenocarcinoma *In-Situ* - AIS; Usual endocervical adenocarcinoma - UEA

Introduction

Gastric type Adenocarcinoma (GAS) is a rare subtype of cervical endocervical adenocarcinoma, classified as a variant of mucinous endocervical adenocarcinoma in the 2014 World Health Organisation (WHO) Classification of Tumours of Female Reproductive Organs. Unlike the more common Usual Endocervical Adenocarcinoma (UEA), GAS is not related to human papilloma virus (HPV), demonstrates more aggressive behaviour, presents at a higher stage, shows unusual patterns of metastasis and has poorer survival outcome as compared to UEA [1]. GAS exhibits a spectrum of differentiation, with Minimal Deviation Adenocarcinoma (MDA) as an extremely well differentiated form.

Emerging evidence suggests that GAS and MDA are malignant entities on a wider spectrum of endocervical glandular lesions exhibiting gastric differentiation (Table 1) [2,3].

Benign	Lobular Endocervical Glandular Hyperplasia (LEGH) Simple gastric (pyloric) metaplasia Tunnel clusters (Type A)
Postulated *in situ* / Pre-malignant	Atypical lobular endocervical glandular hyperplasia (Atypical LEGH) Gastric-Type Adenocarcinoma *In-Situ* (GAIS)
Malignant	Gastric-Type Adenocarcinoma (GAS) Mucinous variant of minimal deviation adenocarcinoma (Adenoma malignum).

Table 1: Endocervical Glandular Lesions Exhibiting Gastric Differentiation.

In particular, over the last decade, a possible in-situ or pre-malignant category has been postulated, namely atypical Lobular Endocervical Glandular Hyperplasia (LEGH) and Gastric-Type Adenocarcinoma *In-Situ* (GAIS). These potential precursors were recognised due to their occurrence in association with MDA and similar immunohistochemically profile for markers of gastric differentiation.

Histologic Features

Atypical LEGH has been used to describe cases of LEGH exhibiting a degree of architectural and/or cytologic atypia without

evidence of stromal invasion. These atypical features include (1) nuclear enlargement; (2) irregular nuclear contour; (3) distinct nucleoli; (4) coarse chromatin texture; (5) loss of polarity; (6) occasional mitotic figures; (7) apoptotic bodies and/or nuclear debris in the lumen and (8) infolding of epithelium or papillary projections with fine fibro vascular stroma [2].

In contrast, GAIS has been used to refer to a lesion in which endocervical glands are replaced by columnar cells showing atypical cytological features similar to atypical LEGH. These include columnar cells with abundant lightly eosinophilic, foamy or bubbly cytoplasm and nuclear atypia that is generally low grade. Goblet cells have also been described (Figure 1A-1C).

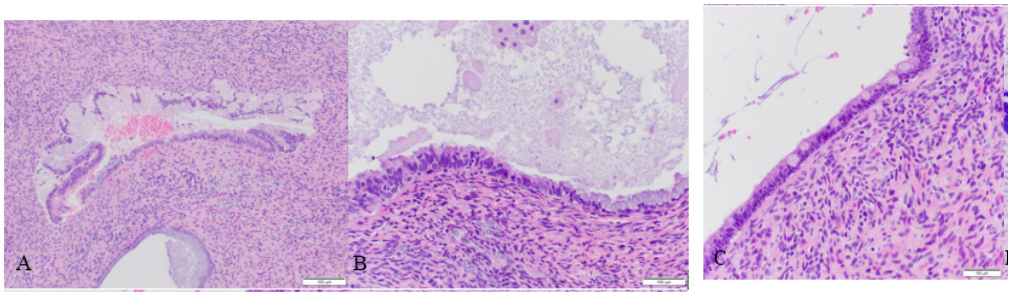

Figure 1: (A) - Abnormal gland showing mild intraglandular complexity (magnification x200). (B) - Areas showing nuclear atypia, with stratified hyperchromatic enlarged nuclei (magnification x400). (C) - Foci of goblet cells (magnification x400).

Unlike atypical LEGH, GAIS retains pre-existing normal glandular architecture, which is different from the lobular architecture of clusters of small glands surrounding a dilated duct typical of LEGH. GAIS sometimes shows intraglandular architectural complexity with small luminal papillary infoldings that may form bridges and cribriform structures. GAIS also shows a distinct topographical location, often arising at the cervical transformation zone in contrast to a high endocervical location as for LEGH [3]. Nonetheless, some authorities have recommended subsuming both atypical LEGH and GAIS under a common umbrella term of "GAIS".

Both atypical LEGH and GAIS demonstrate gastric differentiation histologically, as evidenced by pale cytoplasm that stains red with Alcian blue/periodic Acid - Schiff due to neutral mucins as compared to the purple - violet of acid and neutral mucins in normal endocervical glands (Figure 1D).

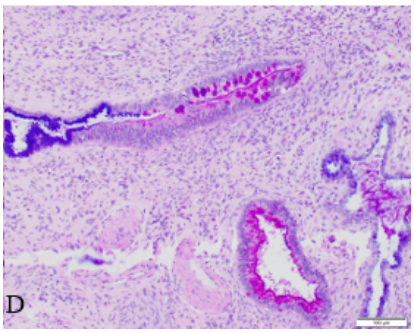

Figure 1: D)- Red cytoplasmic staining contrasting with purple-violet staining of adjacent normal endocervical glands (Alcian blue/PAS stain, magnification x200).

Gastric differentiation is also evidenced by positive staining with HIK1083 and/or MUC6 immunostains. Atypical LEGH, GAIS and GAS are also reported to be positive for CK7 and negative for ER and PR. Being unrelated to HPV, p16 is generally negative or exhibits non block - type staining [4].

Cytologic Features

The characteristic cytologic features of GAS on Papanicolaou (Pap) smears are different from usual adenocarcinoma in-situ/ Usual Endocervical Adenocarcinoma (UEA). Characteristic cytological features of GAS include (a) monolayered and honeycomb sheets; (b) vacuolar and/or foamy cytoplasm, with intracytoplasmic golden-yellow mucin; (c) intracytoplasmic neutrophil entrapment and (d) vesicular nuclei with distinct nucleoli [5]. In comparison, the cytological features of AIS/UEA are well described: (a) crowded hyperchromatic groups with pseudostratified columnar cells and rosette formation; (b) cytoplasmic and nuclear feathering; (c) enlarged nuclei with coarsely granular hyperchromatic chromatin and inconspicuous nucleoli; and (d) mitotic figures and apoptotic bodies. Macronucleoli and tumour diathesis will be seen in UEA.

The cytologic features of gastric-type pre-malignant lesions are not as well described in literature (Table 2).

	Number of cases	Diagnosis on Pap smear	Monolayered and honeycomb sheets	Vacuolar, foamy cytoplasm and intracytoplasmic golden-yellow mucin	Mild nuclear atypia	Intra-cytoplasmic neutrophils
Talia et. al. [6]	6	Atypical glandular cells suggestive of AIS				
Yuan et. al. [7]	2	Atypical glandular cells	Y (Acinar pattern, pseudostratified strips and peripheral palisading also present)	(Variable amounts of golden-yellow mucin. Goblet cells present in one case.)	(Acinar pattern, pseudostratified strips and peripheral palisading also present)	
Tay et. al. [8]	1	Atypical endocervical cells, cannot exclude neoplasia	Y(Focal pseudostratification and peripheral palisading present)	Y(Scattered goblet cells present)	Y(Vesicular nuclei and conspicuous nucleoli)	N
Okuyama et. al. [9]	2	Atypical glandular cells, favour neoplasia	Y(Overlapping glandular cells in clusters showing complicated branching pattern)	Y(Golden-yellow mucin localised on surface of clusters in atypical groups)	Y	
Abbreviations: Y -Present; - Not mentioned; N-Absent.						

Table 2: Summary table of literature on the cytologic features of GAIS.

These lesions are subtler and present a diagnostic challenge on Pap smears. A search on PubMed using the keywords "Gastric-type adenocarcinoma in-situ of the cervix" identified only three case reports and one small series in which the cytological features on Pap smear were detailed. In these cases, the diagnoses on Pap smear were that of atypical glandular cells, ranging from not otherwise specified to favour neoplasia/suggestive of AIS [6-9]. In these reports, monolayered and honeycomb sheets predominate, although overlapping, complicated branching clusters; acinar pattern; pseudostratified strips and peripheral palisading were also present in some. Common to all cases were glandular cells with mucinous cytoplasm, either as golden-yellow mucin or foamy cytoplasm. Goblet cells were present in two cases. Intracytoplasmic neutrophils were not described. Nuclear atypia was present but often low grade or focal, mostly described as vesicular nuclei with conspicuous nucleoli (Figure 2).

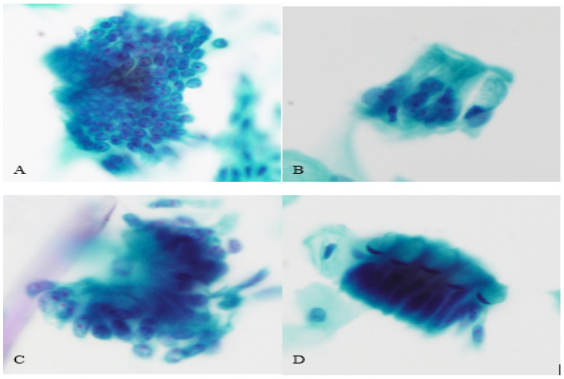

Figure 2: (A) Pap smear shows monolayered sheets of endocervical cells with vesicular nuclei and conspicuous nucleoli (magnification x 400). (B) - The cells showed abundant foamy cytoplasm (magnification x 600). (C) - Pseudostratified palisaded groups of cells and (D) - focal goblet cells were present (magnification x 400). Okuyama et al presented sequential Pap smears in two cases of GAIS, which revealed an interesting finding of localisation of golden-yellow mucin to the surface of glandular clusters preceding development of nuclear atypia. They proposed that this may prove a sensitive finding for early detection of adenocarcinoma arising in LEGH [9].

Discussion & Conclusion

GAS and its precursors are an uncommon but increasingly recognised subtype of endocervical glandular neoplasia. Lesions within this spectrum falling within the category of GAIS are rare and only recently beginning to be characterised. The findings on cytologic smears are subtle and are often classified as atypical glandular cells. Currently, high risk HPV testing may be used to triage smears with borderline endocervical cells, with the implication that these lesions, being non-HPV related, may be missed. Furthermore, moving into the era of HPV vaccination and primary HPV based cervical screening, these lesions are likely to increase in relative incidence and importance. However, as HPV negative cases would not be subject to morphologic analysis, the opportunity to detect GAIS before progression to GAS may be missed. It is hence important for cytotechnologists, cytopathologists, histopathologists as well as clinicians to be aware of the unique etiologic, cytologic and histologic features of these lesions.

Conflict of Interest

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Acknowledgement

Cytology and Histology staff KK Hospital, Singapore.

References

1. Karamurzin YS, Kiyokawa T, Parkash V, Jotwani AR, Patel P, et al. (2015) Gastric-type Endocervical Adenocarcinoma: An Aggressive Tumour with Unusual Metastatic Patterns and Poor Prognosis. Am J Surg Pathol 39: 1449-1457.
2. Mikami Y, Cluggage WG (2013) Endocervical glandular lesions exhibiting gastric differentiation: an emerging spectrum of benign, premalignant, and malignant lesions. Adv Anat Pathol 20: 227-237.
3. Talia KL, Glenn CW (2018) The developing spectrum of gastric-type cervical glandular lesions. Pathology 50: 122-133.
4. Mikami Y, Kiyokawa T, Hata S, Fujiwara K, Moriya T, et al. (2004) Gastrointestinal immunophenotype in adenocarcinomas of the uterine cervix and related glandular lesions: a possible link between lobular endocervical glandular hyperplasia/pyloric gland metaplasia and adenoma malignum. Mod Pathol 17: 962-972.
5. Kawakami F, Mikami Y, Sudo T, Fujiwara K, Hirose T (2015) Cytologic features of gastric-type adenocarcinoma of the uterine cervix. Diagn Cytopathol 43: 791-796.
6. Talia KL, Stewart CJR, Brooke EH, Marisa RN, Mc Cluggage W (2015) Glenn. HPV-negative Gastric Type Adenocarcinoma *In Situ* of the Cervix A Spectrum of Rare Lesions Exhibiting Gastric and Intestinal Differentiation. Am J Surg Pathol 41: 1023-1033.
7. Chang-Tsu Y, Ming-Chieh L, Kuang-Ting K, Tsung-His W, Tsui-Lien M (2016) Gastric-Type Adenocarcinoma in Situ of Uterine Cervix: Cytological and Histopathological Features of Two Cases. Virchows Arch 469: 351-356.
8. Amos T, Mihir G, Kuie LTY, Bing CW, Tan Joyce SL, et al. (2019) A case study of gastric□type adenocarcinoma in situ of the uterine cervix. Cytopathology 30: 265-267.
9. Okuyama R, Hashimoto H, Miura T, Sugita M, Arai M, et al. (2017) Two cases of adenocarcinoma in situ arising in lobular endocervical glandular hyperplasia indicating localization of mucin on the cluster surface as an early cytological finding of malignant transformation. Diagn Cytopathol 45: 842-847.