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Lobular Endocervical Glandular Hyperplasia, a mimicker and potential pitfall for HPV-independent well differentiated Gastric-type Endocervical Adenocarcinoma: Case report and literature review focusing on histology, immunophenotype, and molecular findings

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Abstract

Lobular glandular endocervical hyperplasia is an uncommon benign entity within the spectrum of gastric-type endocervical lesions. We report a case of a 48-year-old woman who presented with a palpable mass and watery vaginal discharge. Ultrasound revealed an 8 cm × 4 cm × 3 cm multicystic mass affecting the cervix, and hysterectomy was performed. The well-delimited multicystic, mucinous mass distorted the entire cervix. Microscopically, endocervical glandular proliferation with a lobular architecture was observed. The glands were lined with a single layer of tall, mucin-rich, columnar cells with basal and bland nuclei. The lesion was positive for MUC6 marker and hormonal receptors were negative, while P53 expression was normal. Three years later, the patient remained disease free. Here, we discuss the differential diagnosis between lobular glandular endocervical hyperplasia and similar conditions, particularly gastric-type endocervical adenocarcinoma, and review the literature focusing on the molecular pathways underlying gastric-type endocervical lesions. This case highlights the importance of accurate diagnosis to ensure favorable outcomes.

Keywords

Lobular endocervical glandular hyperplasia, adenoma malignum, gastric-type endocervical adenocarcinoma, gastric-type endocervical lesions

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Introduction

Lobular endocervical glandular hyperplasia (LEGH) is an uncommon benign glandular proliferation that frequently affects premenopausal women. LEGH is associated with Peutz–Jeghers syndrome and germinal mutations in STK11 gene.[1] Although it usually presents as an incidental finding, well demarcated multicystic masses with watery vaginal discharge rarely occur. Microscopically, LEGH shows a lobular architecture with tall mucinous glands and abundant pale cytoplasm resembling pyloric gastric glands. This condition is the benign form within the spectrum of gastric-type endocervical glandular lesions. Particularly, it has been associated with well differentiated gastric-type endocervical adenocarcinoma (GAS), previously known as adenoma malignum.[1–6] GAS is the primary differential diagnosis upon compatible symptoms and examination findings, as it mimics LEGH. Although a possible transformation from LEGH to GAS has been suggested, there is currently no clear evidence for this event.[7]

Here, we describe an illustrative and challenging case and discuss the following aspects: (1) differential diagnosis and

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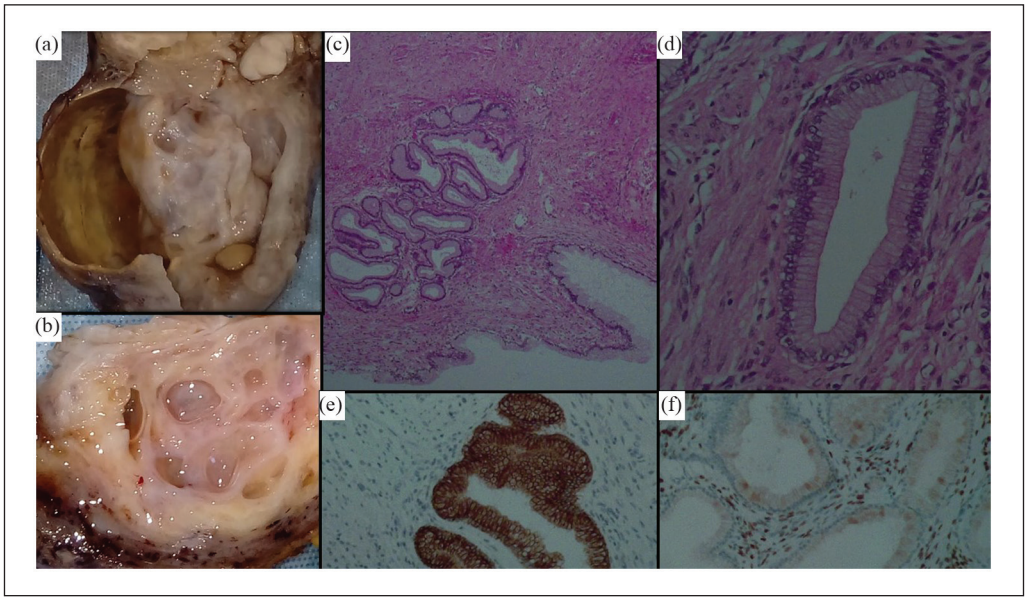

Figure 1. (a) Histerectomy. Muticystic well demarcated mucinous mass with distortion of the cervix. (b) Section of the tumor. (c) HE, 100×. A larger cystic gland surrounded by smaller glands in a lobular configuration. (d) HE, 200×. The glands were lined by a single layer of tall, mucin-rich, columnar cells with basal and bland nuclei (pyloric metaplasia). (e) IHC MUC6. The lesion was positive for MUC6, a typical marker of pyloric glands. (f) IHC Estrogen Receptor. The lesion was negative for estrogen and progesterone receptors.

potential pitfalls of LEGH; (2) immunophenotype, histochemical, and molecular findings associated with LEGH; and (3) possible association with GAS and a likely progressive sequence to malignancy within the spectrum of gastric-type cervical glandular lesions.

Case report

A 48-year-old nulliparous premenopausal woman was referred by her general practitioner due to a palpable mass at the level of the umbilicus together with watery vaginal discharge. The patient had no relevant medical or family history and was otherwise in good health.

Physical examination revealed a mass protruding into the cervical os. Ultrasonography revealed an 8 cm × 4 cm × 3 cm multicystic mass that distorted the entire cervix. Two possible clinical diagnoses were suggested: endocervical adenomyoma and GAS. As the patient manifested not having reproductive wishes and was symptomatic, a simple hysterectomy was performed after discussion.

Macroscopic findings indicated that a well demarcated multicystic mucinous mass affected the entire cervix. (Figure 1(a) and (b)) Microscopic examination showed endocervical glandular proliferation with a strikingly lobular architecture (Figure 1(c)). The lesion mostly affected the inner half of the cervical wall; however, focally, the outer half was also affected. The glands varied in size and were cystic. In some areas, smaller glands surrounded the larger glands in a lobular configuration. Numerous cystic glands are also observed. The glands were lined with a single layer of tall, mucin-rich, columnar cells with basal and bland nuclei. Neither atypia nor mitosis was observed. The stroma did not show desmoplasia and was inconspicuous (Figure 1(d)).

Immunohistochemistry (IHC) was performed, and the lesion was found to be diffusively positive for MUC6 (Figure 1(e)) and negative for estrogen and progesterone receptors (Figure 1(f)). P53 expression showed a wild-type pattern and Ki67 expression was very low (less than 3%). Morphological and immunohistochemical features confirmed the diagnosis of LEGH without atypia. Because this was a benign entity, no further treatment was performed. The patient did not show any disease recurrence after 3 years.

Discussion

Given the characteristics of the reported case, we aim to discuss the following points related to LEGH features and criteria for differential diagnosis.

1. Differential diagnosis and pitfalls: LEGH is a benign glandular proliferation that can mimic other entities, such as tunnel clusters, endocervical adenomyoma (both benign conditions), atypical LEGH (premalignant), gastric-type adenocarcinoma in situ (GAIS, premalignant), and GAS (malignant).[1–7]

The most challenging differential diagnosis are those endocervical premalignant and malignant conditions with gastric metaplasia, as atypical LEGH, GAIS and GAS.

LEGH can show nuclear and architectural atypia, papillary infolding, nuclear hyperchromasia, significant nucleoli,

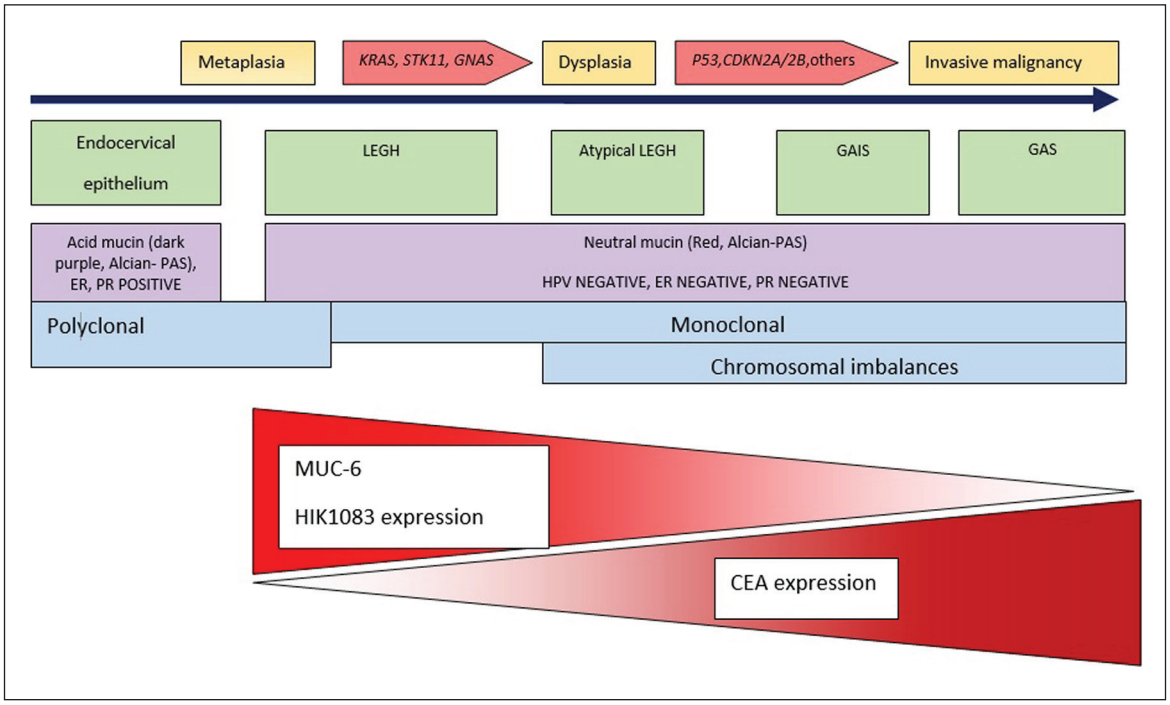

Figure 2. Summary of histochemical characteristics, immunophenotype, and molecular findings in the spectrum of HPV-independent gastric-type endocervical lesions.
LEGH: lobular endocervical hyperplasia; GAIS: gastric-type adenocarcinoma in situ; GAS: well differentiated gastric-type endocervical adenocarcinoma; ER: estrogen receptor; PR: progesterone receptor.

apoptosis, or apical mitosis. This condition is called atypical LEGH and is found more frequently in association with GAS than LEGH without atypia. In addition, chromosomal imbalance (gain of chromosome 3q and loss of 1p) has been observed in both atypical LEGH and GAS.[1,8]

Unlike LEGH, commonly found in the upper cervix, GAIS is typically found at or proximal to the transition zone. Its main characteristic is nuclear atypia. Intestinal differentiation is frequent. Apoptosis and mitosis are observed, although generally inconspicuous. Intraglandular complexity (papillary, cribriform) may occur. Atypical LEGH and GAIS are both premalignant, related conditions. GAIS diagnosis is supported by abnormal P53 expression.[1–5,6]

GAS is the main pitfall of the differential diagnosis from LEGH, and their distinction is sometimes challenging.[1–7] Particularly, extremely well differentiated cases of GAS show similar histological characteristics than those of LEGH. However, clues to differentiate both entities have been described[1–7]: (a) GAS generally shows at least focal atypia; (b) it generally involves the entire cervical wall including the outer wall, in contrast to LEGH, which commonly affects only the inner wall; (c) GAS usually presents as a poorly demarcated lesion, in contrast to LEGH which is usually well delimitated; (d) GAS lacks lobular configuration, in contrast to LEGH which presents with a striking lobular architecture; and (e) GAS can present desmoplasia and lymphovascular invasion. Interestingly, abnormal P53 is seen in approximately half of the GAS cases.[9]

2. Immunophenotype, histochemical, and molecular findings

Gastric metaplastic lesions express pyloric gastric immunohistochemical markers such as MUC6 and HIK1083. Estrogen and progesterone receptors are negative, and the human papilloma virus (HPV) is typically absent.[5,6–7,8] The expression of some markers such as carcinoembryonic antigen, MUC6, HIK1083 and P53 varies from benign to malignant[5,10] (Figure 2).

Interestingly, gastric metaplastic lesions contain neutral mucin, similar to the pyloric-type gastric mucosa. The pyloric-type mucin is stained pale red/magenta with PAS-Alcian blue stain, in contrast to the dark purple/dark blue of acid mucins of the endocervical epithelium.[1,5,8]

Gastric metaplastic lesions have not been addressed in detail from a molecular perspective, and only a few studies are available. In a previous study,[11] five out of nine sporadically tested LEGH cases were monoclonal, and four were polyclonal. This was addressed by the Human Androgen Receptor X-Chromosome Inactivation Assay for Clonality test.

Mutations in *GNAS, KRAS*, and *SKT11* were found in 58% of sporadic LEGHs tested,[12] which were mutually exclusive and were absent in normal endocervical tissue. On the other hand, chromosomal imbalance, such as gain of chromosome 3q and loss of 1p, was found in atypical LEGH and GAS but not in LEGH without atypia.[8]

Next-generation sequencing of 19 patients with GAS[9] showed that *P53* was the most frequently mutated gene,

followed by *MSH6, CDKN2A/B, POLE, SLX4, ARID1A, STK11*, and *BRCA2*. *KRAS* and *GNAS* were found in two and one patient, respectively. Despite the presence of *MSH6* mutations, no alterations in mismatch repair proteins were detected by IHC. Abnormal expression of P53 protein was present in nine cases, but only four of them presented mutations in *P53* gene.

3. Possible association to GAS and the spectrum of gastric-type cervical glandular lesions.

Evidence suggests that malignant transformation can occur from LEGH to GAS (Figure 2). This molecular pathway is HPV-independent and similar to other malignancies of the gastrointestinal tract, such as intraductal papillary mucinous neoplasms (IPMN), which show pyloric-type epithelium, *GNAS* and *KRAS* mutations, and additional mutations in *P53* and *CDKN2A*[13] in progression to adenocarcinoma. This is comparable to molecular alterations observed in the LEGH to GAS progression.[9] Concerning the chromosomal imbalance findings[8] we agree that chromosomal instability is probably the major feature of these cervical adenocarcinomas.

Conclusion

LEGH is a rare and benign entity with a gastric immunophenotype that presents as a multicystic mass in the upper cervix with watery discharge. Caution should be taken upon this set of symptoms, as GAS is the primary diagnosis and its distinction from LEGH could be challenging. Some aspects to differentiate between both entities are atypia, generally present in GAS, at least focally; lobular configuration, only present in LEGH; and lesion limits, which are well delimitated in LEGH, but poorly demarcated in GAS.

Taken together, the reviewed evidence suggests a progressive malignant transformation from LEGH to GAS. The associated molecular pathway is HPV-independent and similar to that of other malignancies of the gastrointestinal tract, such as pancreatic IPMN.

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Author contributions

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Informed consent

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