Review

Discovery Medicine 2026; 38(211): 2375–2383
https://doi.org/10.24976/Discov.Med.202638211.187

Advances in the Diagnostic Evolution and Treatment of Atypical Lobular Endocervical Glandular Hyperplasia

Guoqiu Dong[1,†], Liying Yu[2,†], Xiaoqin Zhang[3], Lifeng Xu[1,*]

[1]Department of Radiology, Tongxiang First People's Hospital, 314500 Tongxiang, Zhejiang, China
[2]Department of Gynecology, Tongxiang Maternal and Child Health Hospital, 314500 Tongxiang, Zhejiang, China
[3]Department of Gynecology, Tongxiang First People's Hospital, 314500 Tongxiang, Zhejiang, China
*Correspondence: XU_LIFENG599@163.com (Lifeng Xu)
[†]These authors contributed equally.
Submitted: 8 June 2026 Revised: 28 July 2026 Accepted: 31 July 2026 Published: 24 August 2026

Atypical lobular endocervical glandular hyperplasia (ALEGH) is a cervical precancerous lesion that develops independently of high-risk human papillomavirus (HPV) infection. It is regarded as a key intermediate stage in the progression from lobular endocervical glandular hyperplasia to gastric-type endocervical adenocarcinoma (G-EAC). Because these lesions are often located in the upper endocervical canal or deep cervical stroma, and their cytological and histological atypia may be subtle, ALEGH is prone to being missed or misdiagnosed in clinical practice. Accurate identification of ALEGH and assessment of its malignant potential are central to improving clinical management. In recent years, advances in multimodal imaging, artificial intelligence (AI)-assisted image analysis, preoperative targeted biopsy, and molecular pathology have provided new evidence for improving preoperative detection and risk stratification. In this review, we summarize the current evidence regarding the imaging diagnosis, preoperative pathological confirmation, molecular mechanisms, and stratified clinical management of ALEGH, with the aim of providing practical reference for early recognition, malignant risk assessment, fertility-preserving decision-making, and surgical management of high-risk ALEGH cases.

Keywords: ALEGH; G-EAC; AI; diagnosis; management

Introduction

Atypical lobular endocervical glandular hyperplasia (ALEGH) is a relatively newly recognized diagnostic entity in gynecologic pathology and remains a considerable clinical challenge. Within the spectrum of cervical glandular lesions, ALEGH has been defined as a pivotal intermediate stage and a key precancerous lesion in the progression from lobular endocervical glandular hyperplasia (LEGH) to invasive gastric-type endocervical adenocarcinoma (G-EAC) and minimal deviation adenocarcinoma [1]. Since this spectrum of lesions was first described by Nucci et al. in 1999 [2], the understanding of cervical adenocarcinoma has undergone a fundamental transition from a morphology-driven concept to an etiology-driven classification. Unlike the majority of usual-type endocervical adenocarcinomas (UEA), which are primarily associated with high-risk human papillomavirus (HPV) infection, ALEGH and related gastric-type lesions follow a distinct HPV-independent carcinogenic pathway and exhibit a characteristic mucinous phenotype with gastric pyloric gland differentiation [3,4].

However, the concealed nature of this HPV-independent carcinogenic pathway poses a substantial challenge for early clinical screening. Because ALEGH is not associated with viral genome integration, currently used HPV DNA-based primary screening strategies are largely ineffective for detecting this type of lesion, and most reported cases show negative HPV nucleic acid test results [5]. In addition, conventional ThinPrep cytologic testing (TCT) is prone to missed diagnosis. On the one hand, ALEGH lesions are usually located deep within the upper endocervical canal, making it difficult for routine sampling brushes to reach the core lesion area [6]. On the other hand, the epithelial cells of ALEGH often retain a certain degree of differentiation, and their nuclear atypia is frequently subtle [7]. As a result, these lesions are often interpreted as negative findings or broadly classified as atypical glandular cells (AGC) in cytological reports, leading to frequent misdiagnosis as physiological Nabothian cysts or benign polyps in clinical practice [6].

This "dual blind spot" in clinical screening stands in sharp contrast to the potentially aggressive outcome associated with ALEGH. With advances in multimodal imaging, minimally invasive diagnostic techniques, and molecular pathology, the clinical management of ALEGH is undergoing substantial changes. Examples include the introduction of the magnetic resonance imaging (MRI) *cosmos pattern* and spatial geometric quantification methods, the development of minimally invasive targeted biopsy approaches

such as hysteroscopy- or endocervicoscopy-guided resection and fractional curettage, as well as the confirmation of monoclonal evolution based on whole-exome sequencing (WES) analysis [8,9]. This review summarizes recent advances in the molecular mechanisms of ALEGH progression, imaging-based quantitative diagnosis, optimization of preoperative minimally invasive biopsy strategies, and risk-stratified individualized management. By integrating current evidence, this review aims to provide a reference for the early identification and management of ALEGH, thereby contributing to the prevention of progression to highly aggressive G-EAC.

Multimodal Imaging Characteristics and Evolution of Differential Diagnosis in ALEGH

Spatial Geometric Quantification and Evolution of MRI-Based Classification Systems

Within the spectrum of gastric-type cervical lesions independent of high-risk HPV infection, MRI is a core imaging modality for the preoperative identification of ALEGH and its differential diagnosis from benign LEGH and malignant G-EAC. Traditional imaging descriptions have mainly focused on multicystic lesions located in the upper endocervical canal or the characteristic cosmos pattern, which refers to a multilocular cystic appearance composed of centrally clustered microcysts surrounded by larger peripheral cysts. This imaging feature shows a specificity of up to 95.5% in distinguishing gastric mucin-positive lesions from physiological Nabothian cysts [6]. However, as pathological progression advances from benign LEGH to atypical ALEGH and ultimately invasive G-EAC, qualitative morphological assessment alone is no longer sufficient for precise clinical stratification. Consequently, imaging evaluation has gradually evolved toward spatial geometric quantification and classification-based predictive systems. According to the 2020 WHO classification system and subsequent imaging studies, the extent of anatomical involvement, the distribution ratio of microcysts, the integrity of the cervical stromal ring, and the presence of solid components are important imaging indicators for assessing the malignant potential of ALEGH [10]. In healthy individuals and patients with LEGH alone, the cervical stromal ring usually appears as a continuous and intact low-signal band. In contrast, local thinning or disruption of the cervical stromal ring is frequently observed in ALEGH and G-EAC owing to stromal infiltration by tumor cells or atypical glands [11].

Quantitative analyses demonstrated that an increased transverse extent of the lesion, significant alterations in the proportion of microcysts within the lesion, and a higher incidence of endometrial involvement were all significantly associated with progression to higher pathological grades. More importantly, the presence of solid components and disrupted cervical stromal rings represents a major distinguishing feature between benign LEGH and ALEGH/G-EAC, as these findings are rarely observed in benign lesions. In addition, longitudinal quantitative MRI studies in follow-up cohorts have shown that the spatial geometric characteristics of ALEGH-associated cystic structures, including maximum cyst diameter and morphological patterns, may change dynamically with increasing age or menopausal transition. These findings suggest that imaging interpretation should be adjusted according to patient age and menopausal status. Representative MRI findings from a patient with pathologically confirmed ALEGH are shown in Fig. 1. The lesion presented as a multilocular cystic structure involving the upper endocervical canal, illustrating the characteristic imaging appearance described above.

Abnormal Blood Flow Characteristics and Three-Dimensional Reconstruction Features of Multimodal Ultrasonography

Although MRI has unique advantages in soft-tissue resolution and spatial stratification, transvaginal multimodal ultrasonography also plays an important role in the preoperative evaluation of ALEGH because of its accessibility and real-time dynamic imaging capability. Compared with benign LEGH, ALEGH exhibits a higher degree of pathological atypia and microvascular remodeling. Therefore, conventional two-dimensional color Doppler ultrasonography often only provides vague evidence of cystic-solid mixed echo patterns in the posterior cervical wall or local regions and has limited ability to detect subtle hemodynamic alterations [12]. Advances in multimodal ultrasonography have partially overcome these limitations. By applying three-dimensional ultrasonographic reconstruction techniques, clinicians are able to reconstruct the internal microcystic architecture of the cervix, closely resembling the MRI cosmos pattern, and clearly demonstrate the spatial relationship between centrally clustered microcysts and surrounding larger cysts. This provides an intuitive morphological basis for the preliminary identification of highly suspected ALEGH cases. Furthermore, the introduction of contrast-enhanced ultrasound (CEUS) enables quantitative evaluation of local microcirculation within the lesion. In areas with malignant transformation or progression to G-EAC, the perfusion kinetics of CEUS microbubble contrast agents often demonstrate a characteristic “rapid enhancement and delayed washout” pattern, and perfusion intensity within the solid or atypical stromal components is significantly higher than that of the surrounding myometrium. These microvascular perfusion characteristics provide important quantitative evidence for preoperative assessment of local invasion depth and selection of subsequent targeted biopsy sites [13].

In addition, both MRI-based geometric quantification and ultrasonographic blood flow assessment still face substantial challenges in clinical practice. Because LEGH,

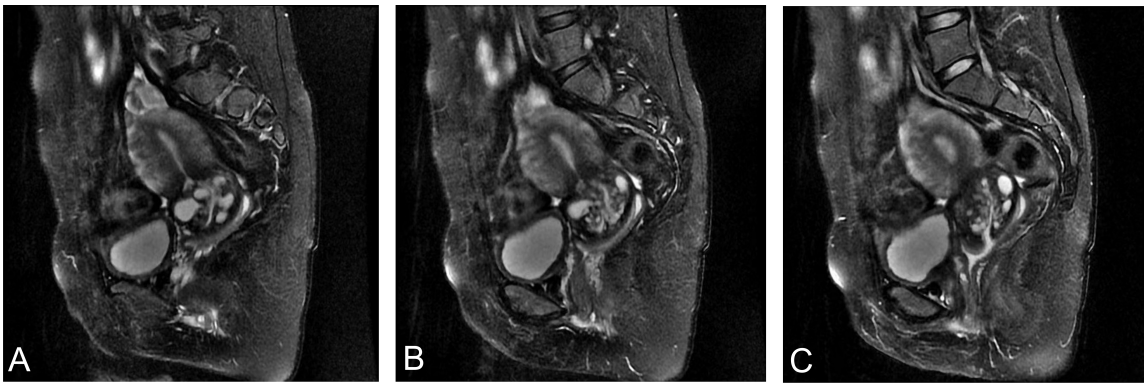

Fig. 1. Representative pelvic MRI findings of ALEGH. (A–C) Sagittal T2-weighted MRI images showing a multilocular cystic lesion involving the upper endocervical canal, with clustered small cysts and a characteristic multicystic architecture suggestive of ALEGH. The images were obtained from a patient treated at Tongxiang First People's Hospital. Written informed consent for publication of the clinical images was obtained from the patient. MRI, magnetic resonance imaging; ALEGH, atypical lobular endocervical glandular hyperplasia.

ALEGH, and invasive minimal deviation adenocarcinoma show considerable morphological overlap across multimodal imaging sequences, visual interpretation is highly susceptible to observer-dependent bias when differentiating benign from malignant lesions. To address this challenge, the integration of artificial intelligence (AI) and deep learning has emerged as an important technological advance in recent years. Recent studies have developed convolutional neural network (CNN)-based AI models for automated lesion segmentation and integrated diagnostic analysis. These models enable fully automated pixel-level lesion segmentation of T2-weighted imaging (T2WI), contrast-enhanced MRI, and ultrasonographic images, exceeding the resolution limits of visual assessment. From a diagnostic perspective, CNN models extract large-scale nonlinear radiomic texture features to quantify subtle spatial heterogeneity within glandular structures, mucin invasion depth, and stromal microvascular distribution. Preliminary studies have suggested that AI-integrated diagnostic approaches may combine macroscopic geometric indicators derived from MRI, such as displacement ratio and longitudinal localization, with CEUS-based microvascular perfusion characteristics, thereby providing additional information for the preoperative assessment of benign and malignant lesions. However, large-scale prospective validation studies are still needed before routine clinical implementation.

Diagnostic Performance and Optimization of Preoperative Minimally Invasive Biopsy Techniques

Limitations of Conventional Cytology and Surface Biopsy and Advances in Multispectral Image Unmixing

Within the spectrum of gastric-type cervical lesions independent of high-risk HPV infection, establishing an accurate preoperative pathological diagnostic pathway remains a major clinical challenge. Conventional screening and biopsy strategies for gynecological malignancies have primarily been developed based on the pathological characteristics of usual-type endocervical adenocarcinoma (UEA). However, when conventional TCT combined with colposcopy-guided multipoint cervical biopsy is applied to ALEGH, a high risk of missed diagnosis has been reported [14]. ALEGH lesions are usually located deep within the upper endocervical canal or cervical stroma, whereas the external cervical os and superficial mucosa often retain a relatively normal appearance. More importantly, atypical glandular epithelial cells in ALEGH frequently maintain a certain degree of differentiation, and their nuclear atypia is often subtle and localized. Consequently, Papanicolaou-stained specimens are easily interpreted as negative findings under routine light microscopy or are broadly classified as atypical glandular cells (AGC) [15].

To overcome the limitations of conventional morphology-based screening, recent advances in digital pathology have introduced multispectral imaging and spectral unmixing technologies, providing a new strategy for improving the sensitivity of preoperative cytological screening [16]. This technique is based on a physical transmission model and employs a 14-channel multispectral system to perform high-dimensional spectral unmixing of cytoplasmic components in Papanicolaou-stained TCT samples. Because ALEGH-specific gastric-type mucin, including pyloric gland-type mucin, exhibits distinct absorbance and chemometric characteristics at specific wavelengths compared with normal endocervical mucus, multispectral quantitative image analysis can directly detect physical alterations in atypical mucin staining within the cytoplasm. This approach enables precise identification of ALEGH-associated signals at the single-cell level and significantly reduces the risk of missed diagnosis caused by the relatively well-differentiated glandular epithelium.

Diagnostic Value of Hysteroscopy- and Endocervicoscopy-Guided Targeted Biopsy

Alongside advances in cytological diagnostic techniques, optimization of histological biopsy pathways is also critical for improving the preoperative diagnosis of ALEGH and preventing malignant progression. Conventional colposcopy-guided superficial biopsy and routine endocervical curettage often fail to obtain representative tissue from lesions located deep within the endocervical canal, resulting in an overall detection rate or pathological concordance rate of less than 10.0% for ALEGH-associated gastric-type glandular lesions [4]. Therefore, hysteroscopy- and endocervicoscopy-guided targeted biopsy under direct visualization has emerged as a minimally invasive sampling approach with high diagnostic value [8]. The application of direct-visualization techniques has transformed the preoperative histological diagnosis of ALEGH from conventional blind sampling toward precise lesion localization and targeted tissue acquisition.

Under the magnified field provided by high-definition cold-light hysteroscopy or endocervicoscopy, operators are able to bypass superficial anatomical barriers and directly access the upper and deeper regions of the endocervical canal. Endoscopically, ALEGH often presents as localized multiple polypoid proliferations of the endocervical mucosa, microcystic protrusions, or a characteristic hypersecretory mucinous phenotype [7]. Direct visualization of the upper and deep endocervical canal facilitates the identification of suspicious lesions that may be difficult to adequately assess using conventional examination methods and enables accurate localization for subsequent targeted biopsy. Under direct visualization, operators can perform targeted biopsy of the most representative areas using miniature biopsy forceps or electrosurgical loops, or undertake local excision of cervical lesions when appropriate, thereby obtaining tissue specimens of sufficient depth that contain stromal components for pathological assessment of architectural disorganization [12]. A previous study has shown that pathological findings obtained through hysteroscopy- or endocervicoscopy-guided targeted biopsy demonstrate good concordance with final diagnoses established from cervical conization or surgical excision specimens, supporting the clinical value of this approach in the preoperative diagnosis of LEGH and ALEGH [8]. Compared with conventional blind sampling, this approach facilitates the acquisition of more representative tissue specimens and may help reduce the risk of missed diagnoses or underestimation caused by inadequate sampling.

Despite these advantages, the diagnostic performance of targeted biopsy may still be influenced by lesion distribution, lesion depth, and sampling adequacy. In multifocal lesions or lesions located predominantly in the deep endocervical canal, inadequate sampling or underestimation of disease extent may still occur. In addition, because ALEGH shares some morphological features with LEGH and gastric-type endocervical lesions, localized biopsy findings may not always fully reflect the overall extent of disease. Therefore, biopsy results should be interpreted in conjunction with imaging findings, pathological assessment, and clinical presentation.

Molecular Pathological Mechanisms and Biomarker Studies in the Malignant Progression of ALEGH

Genomic Mutation Profiles and Monoclonal Evolution Patterns

The progression of cervical glandular lesions from LEGH to ALEGH and eventually to invasive G-EAC or minimal deviation adenocarcinoma is considered a stepwise monoclonal evolutionary process accompanied by the accumulation of specific genetic alterations. Unlike conventional HPV-associated cervical adenocarcinomas, gastric-type lesions are generally considered independent of the oncogenic E6/E7 pathway of high-risk HPV and exhibit distinct molecular genetic features [3]. Recent genomic studies have applied whole-exome sequencing (WES) to spatially distinct LEGH, ALEGH, and G-EAC lesions coexisting in the same patient, allowing reconstruction of the molecular evolutionary trajectory of gastric-type lesions [9]. Inactivation of the STK11 gene, including somatic alterations and germline mutations associated with Peutz–Jeghers syndrome, has been suggested as an early driver event in this progression pathway. Such alterations have been identified not only in advanced malignant lesions but also in a subset of LEGH cases [17]. During the progression from LEGH to atypical LEGH, monoclonal evolution appears to be accompanied by enhanced clonal selection and accumulation of molecular alterations. Mutations in GNAS and KRAS, together with copy number loss or somatic alterations involving tumor suppressor-related genes such as MAP2K4, have been reported more frequently in ALEGH than in LEGH. These findings suggest that ALEGH may represent an important intermediate stage in the transition from benign gastric-type lesions to malignant disease. Further accumulation of molecular alterations at this stage may contribute to subsequent malignant progression. Therefore, early identification and intervention at the ALEGH stage may provide an opportunity for preventing the development of G-EAC.

Gastric-Type Mucin Markers, Latex Agglutination Testing, and Cell-Cycle Regulatory Proteins

In clinical pathology, molecular phenotyping and immunomarker-based assessment are increasingly used to identify the malignant potential of ALEGH at an early stage. This approach has expanded from conventional histochemical staining to body-fluid-based screening and systematic immunohistochemical profiling. Histologically, ALEGH usually shows clear features of gastric pyloric

gland differentiation, with abundant gastric-type mucin in the cytoplasm of glandular epithelial cells. Representative histopathological and immunohistochemical findings are shown in Fig. 2. The lesion demonstrated gastric-type glandular differentiation with positive MUC6 staining, low Ki67 proliferative activity, focal p16 expression, and negative ER/CEA expression, supporting the diagnosis of ALEGH. Immunohistochemical studies by other scholars have shown that the gastric pyloric gland mucin marker MUC6 and its related epitope HIK1083 are often strongly or diffusely expressed in the glandular cytoplasm of ALEGH. In contrast, expression of estrogen receptor (ER) and progesterone receptor (PR) is usually reduced or absent. This immunophenotype helps distinguish ALEGH from HPV-associated usual-type endocervical adenocarcinoma and common benign cystic lesions. However, it should not be described as a single "gold standard"; diagnosis should still be based on morphological findings, clinical features, and additional ancillary tests [3].

Recent clinicopathological follow-up studies have further shown that as lesions progress from LEGH to ALEGH and G-EAC, expression of gastric-type differentiation markers may be accompanied by a change in the staining pattern of CEA, from luminal or apical polarized staining to more extensive cytoplasmic staining. In contrast, common physiological cystic lesions are usually negative for MUC6, HIK1083, and CEA. These immunophenotypic differences may help further characterize atypical glandular lesions that show overlapping or borderline morphological features [18]. To translate these histological and immunophenotypic features into a more clinically accessible screening method, HIK1083-based latex agglutination testing has attracted increasing attention. This assay uses latex particles sensitized with the HIK1083 monoclonal antibody to detect specific carbohydrate structures associated with gastric-type mucin, through an *in vitro* agglutination reaction using cervical mucus or discharge collected from patients. The test is relatively simple to perform, can be completed within a short period, and may therefore have potential value as a clinical screening tool. A previous study has suggested that HIK1083-labeled latex agglutination testing of cervical secretions may help detect gastric-type glandular lesions of the cervix, including LEGH and minimal deviation adenocarcinoma before surgery [19].

In addition, immunohistochemical assessment of cell-cycle-related markers and tumor suppressor proteins may provide useful ancillary information when evaluating proliferative activity and the potential for malignant transformation in ALEGH. As lesions progress from ALEGH to G-EAC, the Ki-67 proliferation index may increase, and the p53 staining pattern may shift from a wild-type pattern to an abnormal pattern. In immunohistochemical interpretation, wild-type p53 expression is usually characterized by heterogeneous and patchy nuclear staining, whereas abnormal p53 expression may present as either diffuse strong nuclear overexpression or complete absence of staining. Complete loss of p53 staining may be associated with alterations leading to truncated or absent protein, while diffuse overexpression is often related to abnormal protein accumulation caused by missense mutations. However, p53 immunohistochemistry should not be regarded as a direct substitute for genetic testing. A previous study has suggested that ALEGH may exhibit a higher Ki-67 labeling index than conventional LEGH and may show abnormal p53 expression, supporting its neoplastic or premalignant nature [20].

However, the Ki-67 index in ALEGH should not be rigidly defined within a fixed range, nor should a single cutoff value be used as the sole criterion for identifying early malignant transformation. In HPV-independent gastric-type lesions, p16 expression typically does not exhibit the diffuse block-type strong positivity observed in HPV-associated adenocarcinoma. Instead, it may exhibit negative, weakly positive, or show focal and patchy staining patterns. Therefore, p16 findings should be interpreted in conjunction with HPV status, morphological features, and other gastric-type markers. Taken together, the expression patterns of Ki-67, p53, and p16 may provide additional information for understanding the biological continuum from ALEGH to G-EAC and may assist in evaluating lesion extent, surgical margin status, and the presence of invasive components in conization or excision specimens.

The molecular evolution of ALEGH and the proposed transition pathway from benign LEGH to G-EAC are summarized in Fig. 3.

Clinical Management Stratification and Fertility Preservation Strategies

The Dual Diagnostic and Therapeutic Value of Cervical Conization and Predictive Models for Residual Disease

For patients with a high preoperative suspicion of ALEGH or those with biopsy findings suggestive of ALEGH, cervical conization plays an important role in both diagnosis and management. Because ALEGH is regarded as a precursor lesion in the development of G-EAC, its distribution within the endocervical canal is often multifocal and difficult to identify completely by limited biopsy sampling. Therefore, preoperative biopsy may underestimate the extent of disease. Conization specimens provide a more comprehensive histological assessment of lesion distribution and may help identify occult malignant transformation [5]. However, residual lesions and postoperative recurrence remain important clinical concerns in patients with ALEGH undergoing conization. Previous follow-up studies have suggested that gastric-type mucin-positive lesions may extend into the upper endocervical canal and deeper stromal regions. Therefore, residual lesions may still be identified in subsequent hysterectomy specimens even after loop excision or cold-knife conization.

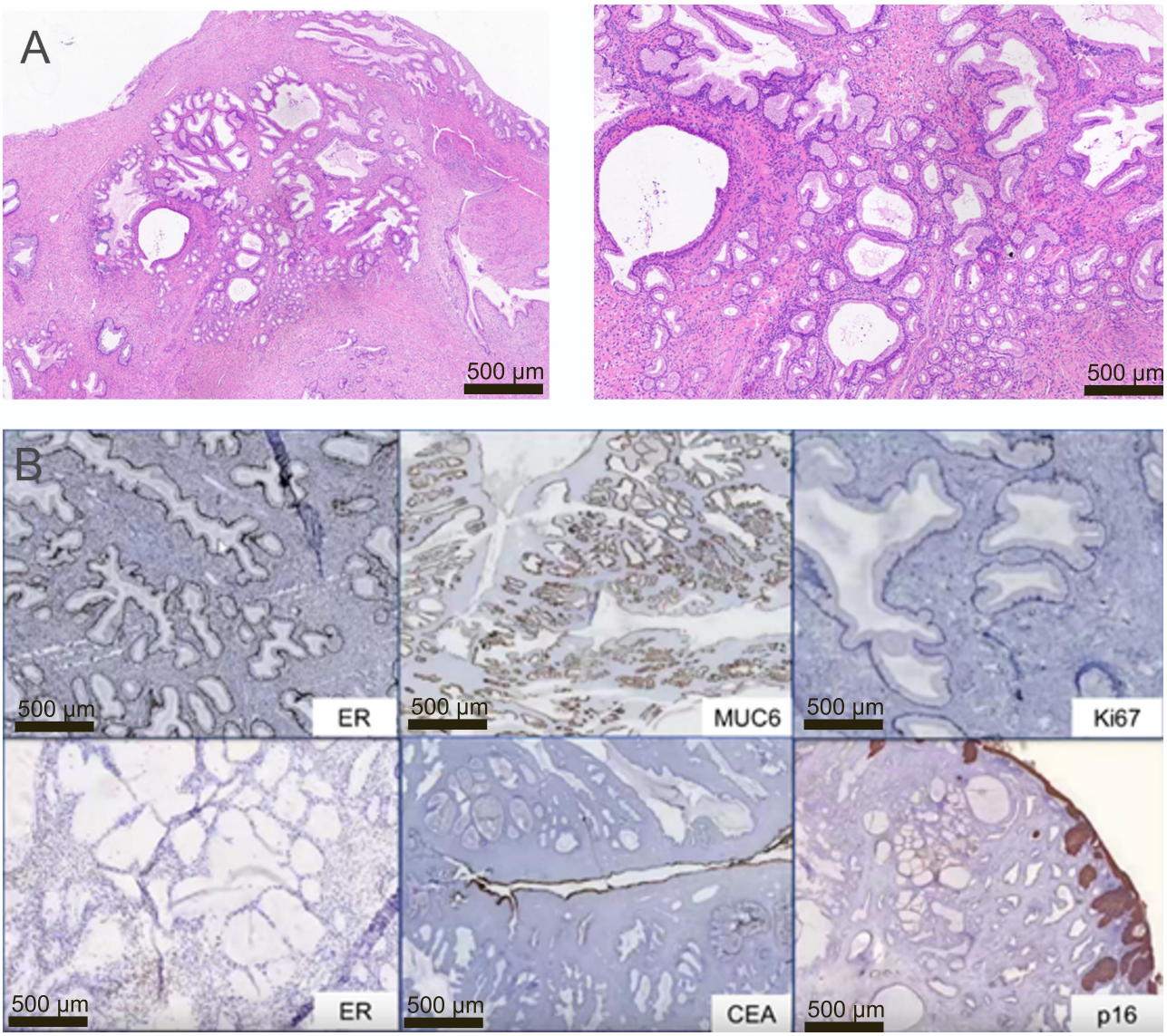

Fig. 2. Histopathological and immunophenotypic characteristics of ALEGH. (A) HE staining demonstrating lobular proliferation of irregular gastric-type glands with mild architectural atypia. (B) Immunohistochemical staining showing MUC6 positivity, low Ki67 proliferative activity, focal p16 expression, and negative ER/CEA expression. The images were obtained from a patient treated at Tongxiang First People's Hospital. Written informed consent for publication of the clinical images was obtained from the patient.

To reduce unnecessary secondary surgery while avoiding missed residual disease, recent studies have focused on identifying factors associated with postoperative persistence or recurrence. In patients with Peutz–Jeghers syndrome, diffuse lesion extent and endometrial involvement on MRI have been associated with more advanced pathological categories and increased malignant potential of cervical glandular lesions [11]. Integration of these clinicopathological and imaging findings may facilitate the development of risk stratification models for postoperative assessment. Such models could support individualized follow-up strategies and assist decision-making regarding additional surgical intervention after conization. The major predictors associated with residual disease risk are summarized in Table 1 (Ref. [5,11]).

Stratified Decision-Making in Reproductive-Age Patients and Advances in Robot-Assisted Precision Surgery for Anatomically Complex Cases

When establishing a long-term management plan for ALEGH, clinical decisions should take into account the patient's age, menopausal status, risk profile, and reproductive wishes. For patients who have completed childbearing, are of advanced age, or have high-risk features such as STK11 mutations associated with Peutz–Jeghers syndrome, total hysterectomy is often considered a definitive option, given the potential for occult progression from ALEGH to G-EAC [17]. For younger reproductive-age patients who strongly wish to preserve fertility, conservative management after cervical conization may be considered under

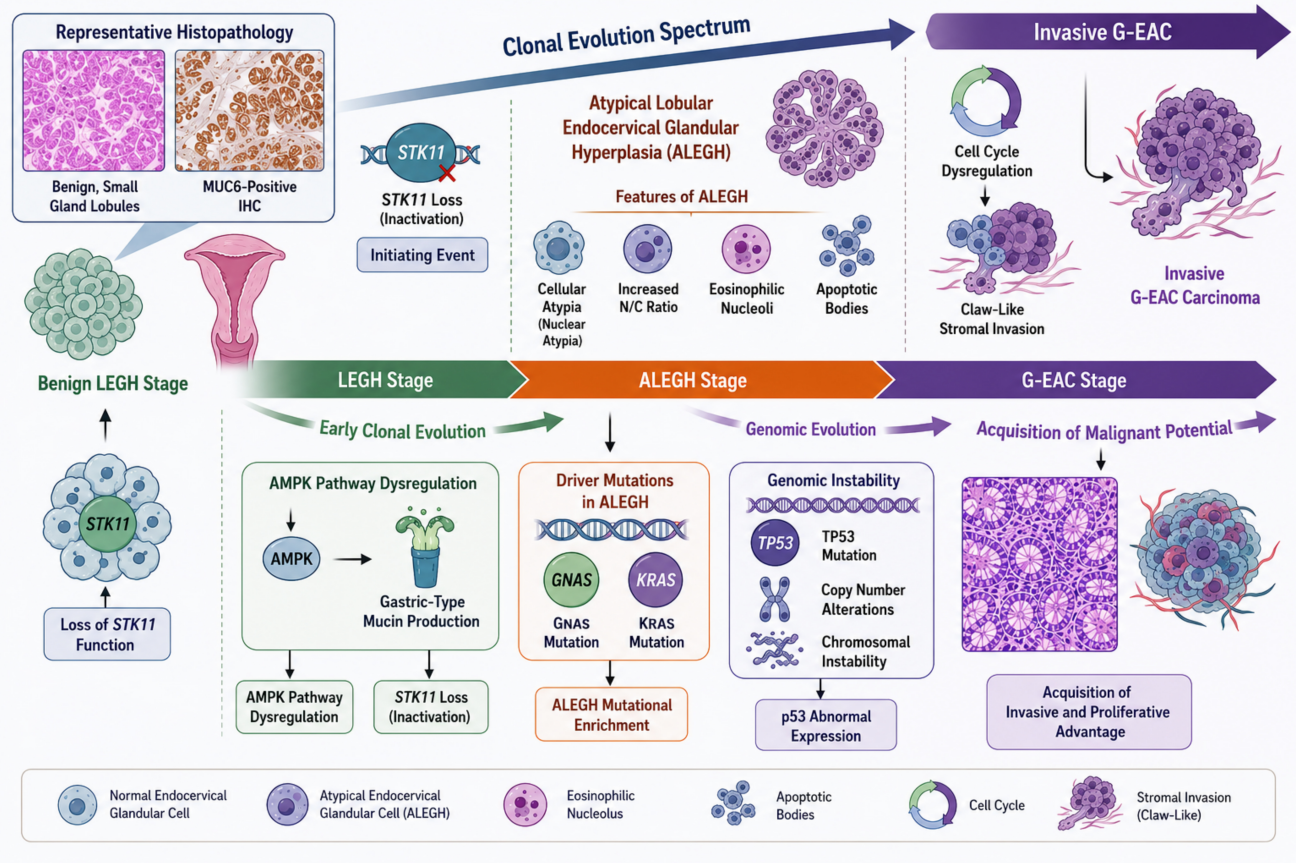

Fig. 3. Proposed clonal evolution model and molecular progression pathway from LEGH to ALEGH and gastric-type endocervical adenocarcinoma. LEGH, lobular endocervical glandular hyperplasia; G-EAC, gastric-type endocervical adenocarcinoma. The conceptual design, scientific content, and original materials were developed by the authors. GPT 5.0 was used as an AI-assisted tool for graphical refinement and visualization during figure preparation.

Table 1. Potential predictors associated with residual disease or higher-risk clinical features after conization in ALEGH.

Predictor	Clinical implication	Supporting evidence
Positive surgical margins	May indicate incomplete excision and increased residual disease risk	ALEGH lesions are often located high in the endocervical canal, making positive margins common after conization [5].
Lesion depth / deep endocervical location	May increase the risk of inadequate sampling or incomplete removal	ALEGH is often difficult to completely assess or remove because of its high/deep cervical location [5].
Larger MRI extent	May suggest broader lesion distribution and higher malignant potential	MRI findings such as enlarged cystic lesion areas, solid components, or invasive boundaries may suggest malignant transformation [5].
Solid component or invasive boundary on MRI	May indicate progression toward malignant disease	MRI grading studies assess cervical lesion pathology using imaging features and potential malignancy [11].

MRI, magnetic resonance imaging.

carefully selected conditions. These may include negative surgical margins and no abnormal p53 expression. Such an approach should only be adopted after thorough counseling and informed consent, with close postoperative surveillance. Follow-up may include serial assessment of cervical mucus using the HIK1083 latex agglutination test, together with regular high-resolution MRI to monitor residual or recurrent lesions. This combined approach may help balance the need to detect malignant progression early with the goal of fertility preservation.

In patients undergoing definitive radical surgery or total hysterectomy, advances in minimally invasive surgical techniques may provide additional safety in anatomically complex cases. This is particularly relevant for patients with rare pelvic anomalies, such as uterus didelphys with unilateral ALEGH, or for those with severe adhesions after repeated cervical procedures. In such settings, conventional laparoscopy may be limited by distorted anatomy and restricted visualization. Recent clinical reports have described the use of robot-assisted total hysterectomy in selected complex cases [21]. The robotic platform provides a three-dimensional magnified surgical view and highly controlled instrument movement, allowing more precise dissection around the cervix, parametrial tissues, ureters, and bladder. Preoperative MRI findings can also be reviewed intraoperatively to facilitate correlation between imaging characteristics and the operative field, particularly when lesion distribution or pelvic anatomy is unusual. This image-informed surgical approach may improve intraoperative orientation and support more complete removal of ALEGH lesions while reducing the risk of injury to adjacent pelvic structures.

Conclusion

In recent years, research on ALEGH has gradually expanded beyond conventional histopathological assessment to encompass quantitative imaging analysis, molecular pathological mechanisms, and precision surgical management. Current evidence generally supports that ALEGH represents a distinct gastric-type precursor lesion with limited association with high-risk HPV infection and serves as an important intermediate stage in the progression from LEGH to G-EAC. From a clinical perspective, advances in multimodal imaging have substantially improved the detection and characterization of ALEGH. MRI provides valuable information regarding lesion distribution, cystic–solid architecture, and the extent of deep tissue involvement, while contrast-enhanced ultrasonography (CEUS) offers additional assessment of hemodynamic features. Together, these approaches provide objective information for differentiating benign from malignant lesions. Looking forward, continued development of radiomics, deep learning, and multimodal artificial intelligence algorithms may further enhance preoperative risk stratification and diagnostic performance.

In the field of minimally invasive diagnosis and precision surgery, the management of ALEGH is gradually shifting from conventional blind sampling toward targeted tissue acquisition under direct visualization. Techniques including hysteroscopy- and endocervicoscopy-guided biopsy, multispectral cytological analysis, and molecular marker detection have provided new opportunities to improve lesion identification. In the future, integration of molecular imaging technologies with robot-assisted surgical platforms may further improve lesion localization and resection accuracy in anatomically complex cases while supporting fertility-preserving management. At the molecular level, whole-exome sequencing (WES)-based studies have begun to clarify the clonal evolutionary continuum linking LEGH, ALEGH, and G-EAC. Future investigations incorporating single-cell sequencing and spatial transcriptomics may provide deeper insights into STK11-associated signaling abnormalities, tumor microenvironment remodeling, and mechanisms of immune escape, thereby contributing to earlier intervention strategies and more precise therapeutic approaches for preventing malignant progression.

Overall, advances in imaging, cytology, targeted biopsy, and molecular pathology are gradually refining the diagnostic and management framework for ALEGH. The integration of these complementary approaches may facilitate earlier detection, more accurate risk assessment, and more individualized clinical decision-making. As understanding of the biological behavior of ALEGH continues to evolve, risk-adapted management strategies may help optimize patient outcomes and reduce the risk of progression to gastric-type endocervical adenocarcinoma.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

GQD and LFX conceived the idea for the review and developed the manuscript outline. LYY and XQZ performed the literature search, collected and organized the relevant references, and prepared the first draft of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Tongxiang First People's Hospital (Approval No. 2026-011). Written informed consent was obtained from the patient for participation and publication of the clinical data and images. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Acknowledgment

Not applicable.

Funding

This research received no external funding

Conflict of Interest

The authors declare no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

The authors conceived and created the initial draft of the Fig. 3, and AI (ChatGPT 5.0) was subsequently used to optimize the figure, including graphical enhancement, stylistic refinement, layout optimization, and limited text editing. All scientific content, biological pathways, annotations, and interpretations were determined by the authors. The final figure was carefully reviewed and approved by the authors, who accept full responsibility for its accuracy.

References

[1] Miyamoto T, Kobara H, Shiozawa T. Biology and management of lobular endocervical glandular hyperplasia. The Journal of Obstetrics and Gynaecology Research. 2022; 48: 3056–3067. https://doi.org/10.1111/jog.15441

[2] Nucci MR, Clement PB, Young RH. Lobular endocervical glandular hyperplasia, not otherwise specified: a clinicopathologic analysis of thirteen cases of a distinctive pseudoneoplastic lesion and comparison with fourteen cases of adenoma malignum. The American Journal of Surgical Pathology. 1999; 23: 886–891. https://doi.org/10.1097/00000478-199908000-00005

[3] Molero A, Parra A, Blanco I, Ascensión A, Ortega P. 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. SAGE Open Medical Case Reports. 2023; 11: 2050313X231186210. https://doi.org/10.1177/2050313X231186210

[4] Fu S, Ge W, Sun X, Lin H. Clinicopathological analysis of 12 cases of typical and atypical lobular endocervical glandular hyperplasia. Zhejiang Clinical Medical Journal. 2025; 27: 593–595. (In Chinese)

[5] Wan Z, Liu S, Sang N, Tang Y, Wen P, Zhang P, et al. Atypical lobular endocervical glandular hyperplasia: two case report and literature review. Frontiers in Oncology. 2023; 13: 1298793. https://doi.org/10.3389/fonc.2023.1298793

[6] Ohya A, Fujinaga Y. Lobular Endocervical Glandular Hyperplasia and Related Glandular Disorders: Current Status of Diagnosis with MR Imaging. Magnetic Resonance in Medical Sciences : MRMS : an Official Journal of Japan Society of Magnetic Resonance in Medicine. 2025; 24: 332–342. https://doi.org/10.2463/mrms.rev.2024-0198

[7] Ge Z, Wang X, Zhang Z, Li J, Jiang C, Luo T. Synchronous atypical lobular endocervical glandular hyperplasia of the cervix and endometrium: a clinicopathologic case report and review of literature. Journal of Medical Case Reports. 2026; 20: 191. https://doi.org/10.1186/s13256-026-05906-2

[8] Shiro R, Kotani Y, Ohta M, Sato H, Kashima Y, Murakami K, et al. Diagnostic Utility of Hysteroscopic Biopsy in Cases of Suspected Lobular Endocervical Glandular Hyperplasia and Comparison with Cervical Conization. Healthcare (Basel, Switzerland). 2023; 11: 1619. https://doi.org/10.3390/healthcare11111619

[9] Kuruma A, Masuda T, Sato K, Kido K, Motooka D, Komura N, et al. Identification of the Carcinogenic Process from Lobular Endocervical Glandular Hyperplasia to Gastric-Type Adenocarcinoma of the Uterine Cervix via Whole-Exome Sequencing. Cancers. 2026; 18: 651. https://doi.org/10.3390/cancers18040651

[10] Höhn AK, Brambs CE, Hiller GGR, May D, Schmoeckel E, Horn LC. 2020 WHO Classification of Female Genital Tumors. Geburtshilfe Und Frauenheilkunde. 2021; 81: 1145–1153. https://doi.org/10.1055/a-1545-4279

[11] Jiang A, Chen Y, Ning Y, Yu B, Wang H, Ma F, et al. MRI grading for informed clinical decision-making in Peutz-Jeghers syndrome patients with cervical lesions. Scientific Reports. 2024; 14: 23731. https://doi.org/10.1038/s41598-024-75227-1

[12] Tang S, Jiang X, Wang X. Lobular endocervical glandular hyperplasia: Two case report and literature review. Medicine. 2024; 103: e40968. https://doi.org/10.1097/MD.0000000000040968

[13] Yang L, Duan D, Xiong Y, Liu T, Zhao L, Lai F, et al. Preoperative multimodal ultrasonic imaging in a case of Peutz-Jeghers syndrome complicated by atypical lobular endocervical glandular hyperplasia: a case report and literature review. Hereditary Cancer in Clinical Practice. 2024; 22: 3. https://doi.org/10.1186/s13053-024-00275-7

[14] Chen S, Tao X, Zhang H, Feng W, Li Q. Analysis of 13 cases of lobular endocervical glandular hyperplasia. Chinese Journal of Practical Gynecology and Obstetrics. 2018; 34: 285–289. https://doi.org/10.19538/j.fk2018030113 (In Chinese)

[15] Liu Y, Zhang H. Report of two cases of minimal deviation adenocarcinoma of the cervix and atypical lobular endocervical glandular hyperplasia. Journal of Shandong First Medical University. 2023; 44: 130–133. (In Chinese)

[16] Takeyama S, Watanabe T, Gong N, Yamaguchi M, Urata T, Kimura F, et al. Dye amount quantification of Papanicolaou-stained cytological images by multispectral unmixing: spectral analysis of cytoplasmic mucin. Journal of Medical Imaging (Bellingham, Wash.). 2025; 12: 017501. https://doi.org/10.1117/1.JMI.12.1.017501

[17] Ichinose T, Takasaki K, Takahashi Y, Hirano M, Nishida H, Hiraike H, et al. Lobular endocervical glandular hyperplasia diagnosed during surveillance for Peutz-Jeghers Syndrome: A case report. Gynecologic Oncology Reports. 2025; 57: 101673. https://doi.org/10.1016/j.gore.2024.101673

[18] Fulgione C, Raffone A, Travaglino A, Arciuolo D, Santoro A, Cianfrini F, et al. Diagnostic accuracy of HIK1083 and MUC6 as immunohistochemical markers of endocervical gastric-type adenocarcinoma: A systematic review and meta-analysis. Pathology, Research and Practice. 2023; 241: 154261. https://doi.org/10.1016/j.prp.2022.154261

[19] Omori M, Hashi A, Ishii Y, Yuminamochi T, Nara M, Kondo T, et al. Clinical impact of preoperative screening for gastric mucin secretion in cervical discharge by HIK1083-labeled latex agglutination test. American Journal of Clinical Pathology. 2008; 130: 585–594. https://doi.org/10.1309/L8XME5JVEJ74C3F1

[20] Mikami Y, Kojima A, Kiyokawa T, Manabe T. Ki67 labelling index and p53 status indicate neoplastic nature of atypical lobular endocervical glandular hyperplasia (ALEGH). Histopathology. 2009; 55: 362–364. https://doi.org/10.1111/j.1365-2559.2009.03346.x

[21] Nagata H, Komatsu H, Nakaso T, Kudoh A, Azuma Y, Taniguchi F. Robot-Assisted Total Hysterectomy of Extremely Unusual Pelvic Anatomy: A Case Report and Literature Review. Yonago Acta Medica. 2022; 65: 315–319. https://doi.org/10.33160/yam.2022.11.003