

INVASIVE STRATIFIED MUCIN-PRODUCING INTRAEPITHELIAL LESION (iSMILE) IN A HIGH-RISK PATIENT: DIAGNOSTIC AND MANAGEMENT CHALLENGES

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ABSTRACT

Background: Invasive stratified mucin-producing carcinoma (iSMILE) is a rare HPV-associated subtype of endocervical adenocarcinoma, representing the invasive counterpart of stratified mucin-producing intraepithelial lesion (SMILE). Its overlapping squamous and glandular features often result in diagnostic difficulty.

Case Presentation: A 49-year-old G2P2 HIV-positive woman on HAART presented with a high-grade squamous intraepithelial lesion on Pap smear. Colposcopic findings were suspicious for microinvasion, and a cone biopsy revealed HPV-associated SMILE with invasive components, lymphovascular invasion, and margins were positive. Following multidisciplinary team (MDT) discussion, the patient underwent a class III radical hysterectomy with bilateral pelvic lymph node dissection. Final histopathology confirmed invasive stratified mucin-producing carcinoma measuring 3 × 2.5 mm with a 7 mm depth of invasion, negative lymphovascular space invasion, clear parametria, and negative lymph nodes. Immunohistochemistry was positive for p16 and PAS-D. The disease was staged as FIGO IB2 (FIGO 2018 staging), and no adjuvant therapy was indicated as per the MDT consensus.

Conclusion: This case illustrates the diagnostic challenges posed by SMILE and iSMILE and highlights the importance of cone biopsy and comprehensive pathological evaluation to exclude invasive disease before definitive treatment.

Introduction

Stratified mucin-producing intraepithelial lesion (SMILE) is a rare, HPV-associated high-grade cervical lesion arising in the transformation zone that may coexist with other precancerous lesions or progress to an aggressive invasive form (iSMILE). It resembles HSIL histologically but is distinguished by mucin-rich, stratified glandular cells and characteristic immunohistochemical markers^[1,2,3]. Management typically involves excision with confirmation of non-invasion before more extensive surgery, while invasive cases require multidisciplinary care; however, knowledge remains limited due to its rarity.

Case Presentation

A 49-year-old, G2P2, HIV-positive woman on HAART (viral load: <50 copies/mL, CD4: 588 cells/μL), presented with a high-grade squamous intraepithelial lesion (HSIL) on cytology.

Colposcopy: features suggestive of microinvasion (mosaicism, punctuations and abnormal vessels)

Hot loop Cone in 3 scoops (anterior, posterior and endocervical) under GA

Histology: HPV-associated SMILE with invasive components, lymphovascular invasion, and margins were positive for Squamous Cell Carcinoma (SCC),

Histology Reviewed and staged at least FIGO IB2 (2009), and planned for Radical Hysterectomy and Bilateral Pelvic Lymphadenectomy

Pre-Operative analysis: normal blood values and no evidence of metastases

Final histology: no post-operative high- or intermediate-risk factors (according to Peters and Sedlis criteria), she was planned for follow-up only- via colposcopy and cytology- without adjuvant therapy.

Results

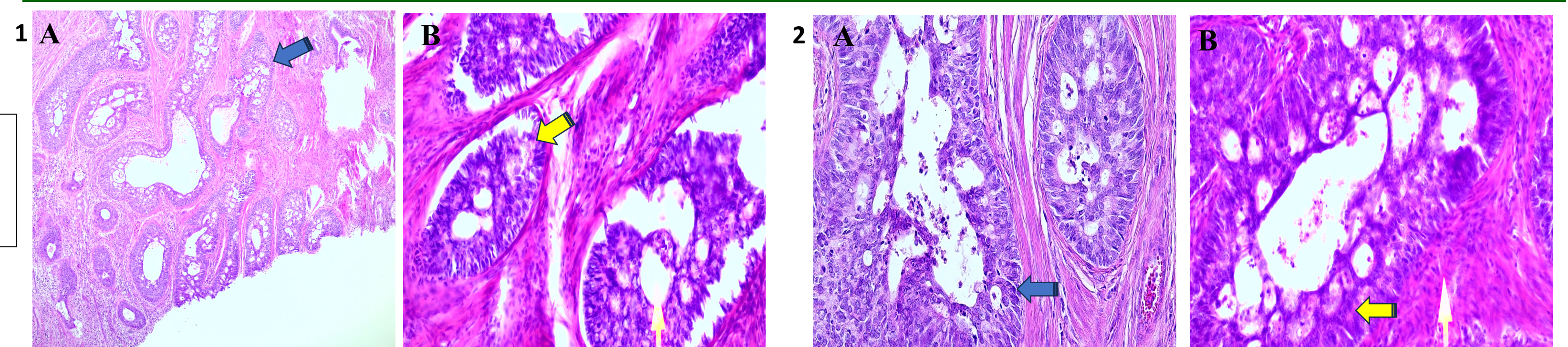


Fig. 1 (A – B): Photomicroscopy of iSMILE after H & E staining. Nests and solid sheets with stratified squamous epithelium with overlying mucinous epithelium [blue arrow] (A). Tumor cells have abundant intracytoplasmic mucin [yellow arrow]. (B) Magnification; 40 X and 200 X of the original, respectively.

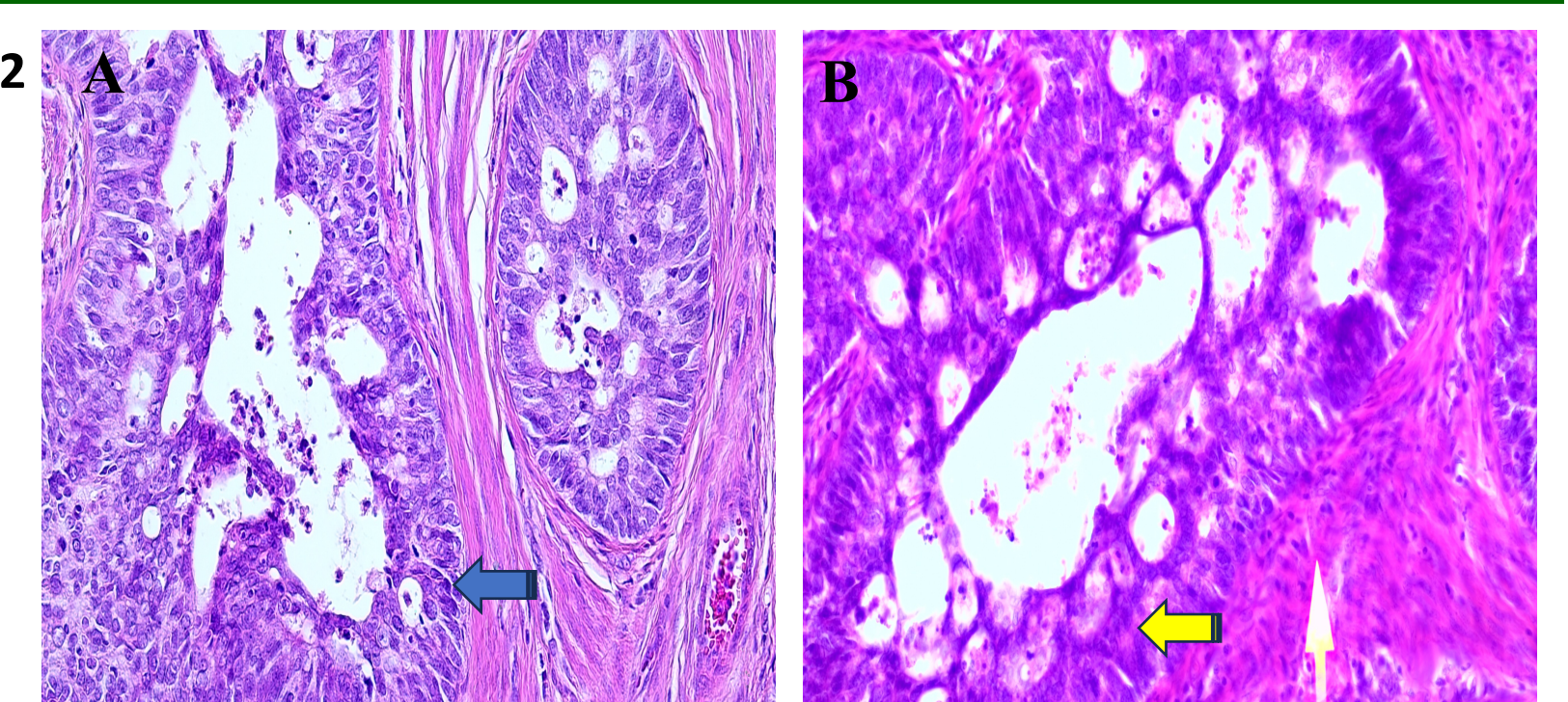


Fig. 2 (A – B): High power microscopy views H & E staining. Stratified epithelium with cells showing cytologic atypia [blue arrow], (A) nests of mucinous epithelium are seen [yellow arrow]. (B) Magnification; 200 X and 400 X of the original, respectively.

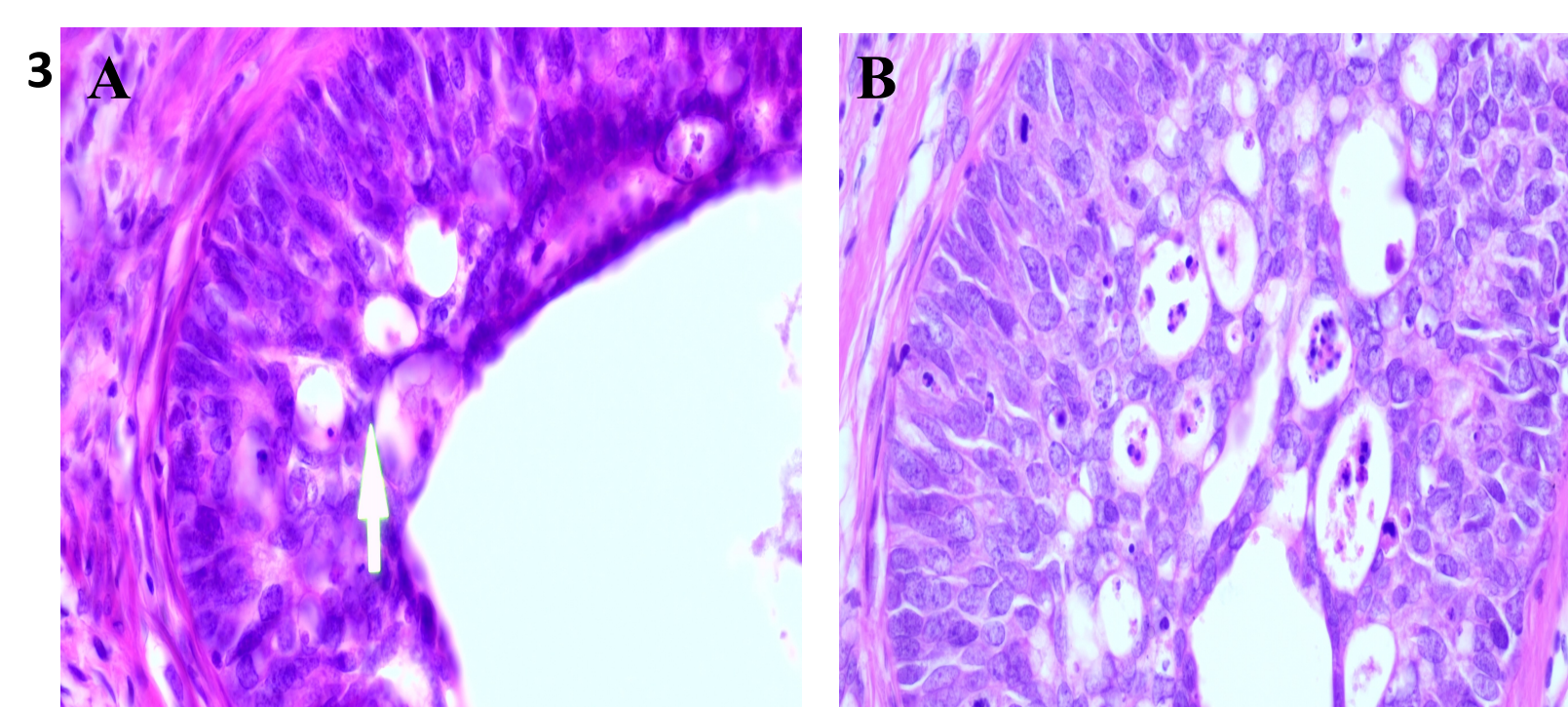


Fig. 3 (A – B): Photomicroscopy of iSMILE H & E staining. High power microscopy demonstrating tumor cells with abundant intracytoplasmic mucin vacuoles [white arrow] (A), and atypical cells with brisk mitoses and apoptotic bodies [yellow arrow] (B). Magnification; 400 X of the original.

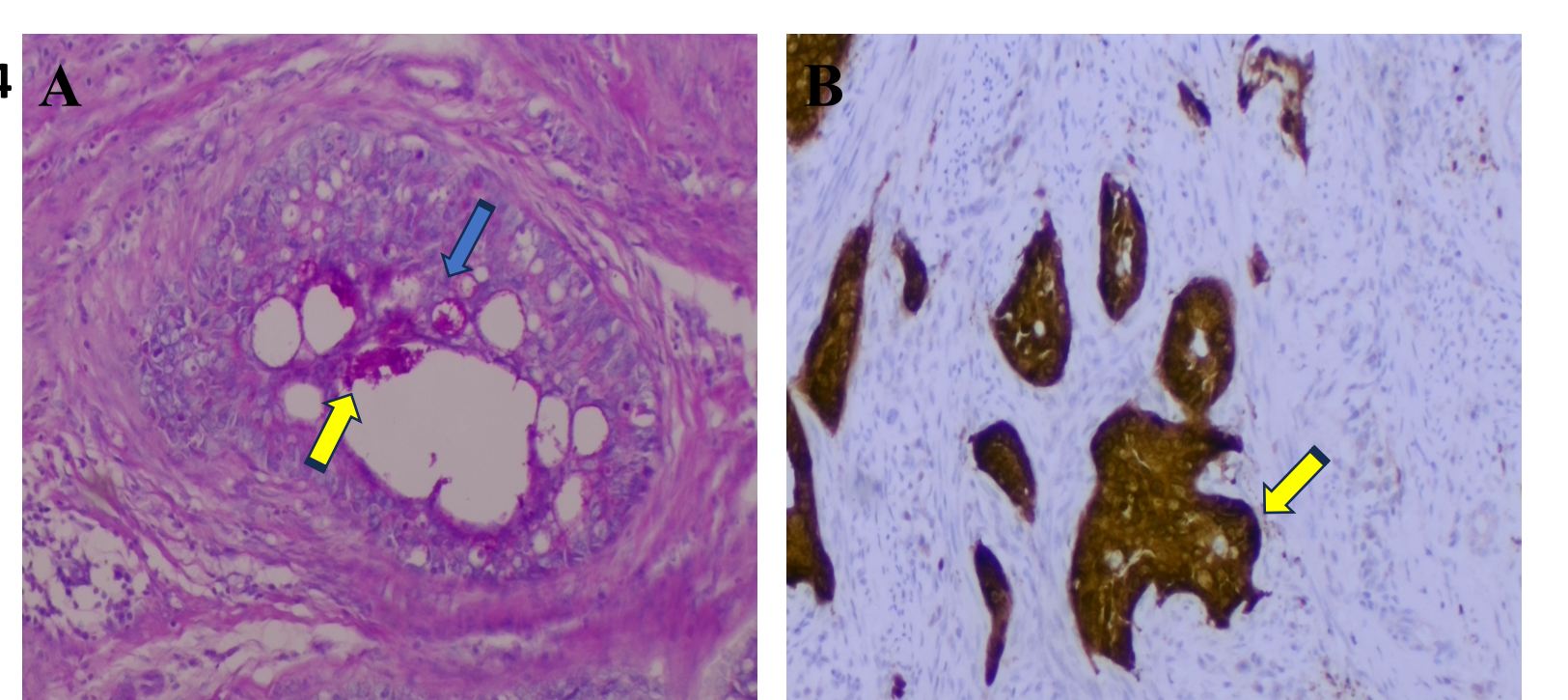


Fig. 4 (A – B): Photomicroscopy of iSMILE after special immunohistochemical staining with PAS-D (mucin) and immunohistochemical stain p16. High power microscopy demonstrating intracellular mucin production [blue arrow] and luminal mucin deposition [yellow arrow] (A). Overexpression of p16, demonstrating invasive tumour nests [yellow arrow] (B). Magnification: 400X

Discussion

	Discussion
SMILE	Similarity and differences to Other Pre-invasive Lesions <i>Classified as a variant of Adenocarcinoma in situ (AIS). It exhibits architectural features that encompass cellular stratification, mimicking a squamous intraepithelial lesion (SIL), with crowding, an increased nuclear-to-cytoplasmic ratio, hyperchromasia, mitoses, and apoptosis^[1-2]. Furthermore, SMILE has abundant intracytoplasmic mucin vacuoles</i>
iSMILE	iSMILE is an aggressive component of SMILE <i>“SMILE is reported as a precursor for iSMILE”, our report shows SMILE in a background of SCC on a cone specimen. Similar to other reports where its associated with HSIL, AIS or combination. Final histology of hysterectomy specimen shows iSMILE. iSMILE behaves more aggressive than AIS</i>
Diagnosis	IHC expression (SMILE vs. iSMILE) <i>“strong P16 expression (HPV association-SIL & AIS) and abundant mucin</i>
Management	Standard of care for SMILE is Conization or Hysterectomy depending on fertility desires¹ <i>Cone biopsy is necessary before management is offered to R/O iSMILE. Our present case, Radical hysterectomy was done due to additional risk factors on the cone specimen. Coincidentally, iSMILE was diagnosed on the final histology.</i> <i>“The diagnosis of SMILE and iSMILE is difficulty since phenotypically lie within the boundary of squamous & glandular intraepithelial neoplasia, features initially reported as HSIL or AIS thus misdiagnosis and underreporting.</i>

Cases with squamous and glandular intraepithelial neoplasia require excisional procedure (LEEP/Cone), proper immunostaining and MDT, with a gynecology pathologist to review histology before undergoing definitive management

Conclusion

- The diagnosis of SMILE or iSMILE poses a challenge, since it straddles the phenotypic boundary between squamous and glandular intraepithelial neoplasia, features of which have previously been reported as AIS or HSIL.
- This suggests that even though these lesions are uncommon, their features have also suffered due to misdiagnosis, thus underreporting.
- Thus, all cases with such features require a loop electrosurgical excision procedure (LEEP) or cone biopsy, and a multidisciplinary team, including a gynecologic oncologist, medical oncologists, and a gynecologic cytopathologist, to review the histology before undergoing definitive treatment, and final histology to be reviewed after surgery. Additionally, proper immunostaining would suffice to identify these rare and uncommon cases, hence proper management.

References

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COI Disclosure

I have no financial relationships to disclose.