

# Persistent High-Grade Dyskaryosis in cytology with Low-Grade Histology in a Patient with Vaginal Adenosis and Unusual Cervical Gastric Metaplasia: A Long-Term Diagnostic Challenge

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# Background

- Persistent high-grade cervical cytology with consistently low-grade or negative histology represents a well-recognised challenge in cytopathology and clinical management.
- Careful evaluation is required to avoid both under- and overtreatment.
- Separately, in utero exposure to diethylstilbestrol (DES) has long been linked to vaginal adenosis and an increased lifetime risk of clear cell adenocarcinoma.
- However, not all glandular changes observed in DES-exposed individuals are malignant or premalignant, and understanding these benign variants is essential in guiding management.
- Originally marketed as a “miracle drug” in the 1940s and 1950s, DES was widely prescribed to prevent miscarriage and other pregnancy complications (Apfel & Fisher, 1984). Its long-term consequences, however, have become well established over subsequent decades.

## Case Presentation:

- We present a complex case involving both a likely DES-associated glandular abnormality and persistent cytology-histology discordance, necessitating multidisciplinary evaluation over a long period of time.
- A woman in her mid-fifties, with probable maternal DES exposure, has been under gynaecological follow-up for 17 years.
- Vaginal biopsies confirmed vaginal adenosis.
- A hysterectomy specimen also showed features in keeping with vaginal adenosis.

## Histological findings - glandular abnormality

- In one of the cervical loop excision specimens(LLETZ) , endocervical glands exhibited a lobular architecture with intestinal-type morphology. These glands displayed no significant cytological atypia, and mitotic activity was not identified.

Immunohistochemistry revealed:

- **Negative staining** for p16, oestrogen receptor (ER), and progesterone receptor (PR)
- **Focal, patchy positivity** for carcinoembryonic antigen (CEA)
- **p53** showed weak, wild-type staining (non-mutant pattern)
- **Ki-67** proliferation index was low.
- **Carbonic anhydrase IX (CAIX)** staining was weak within the intestinal-type glands
- The possibility of an HPV-independent in situ glandular lesion with intestinal differentiation was considered. Given the rarity of such lesions, the case was referred for expert review.

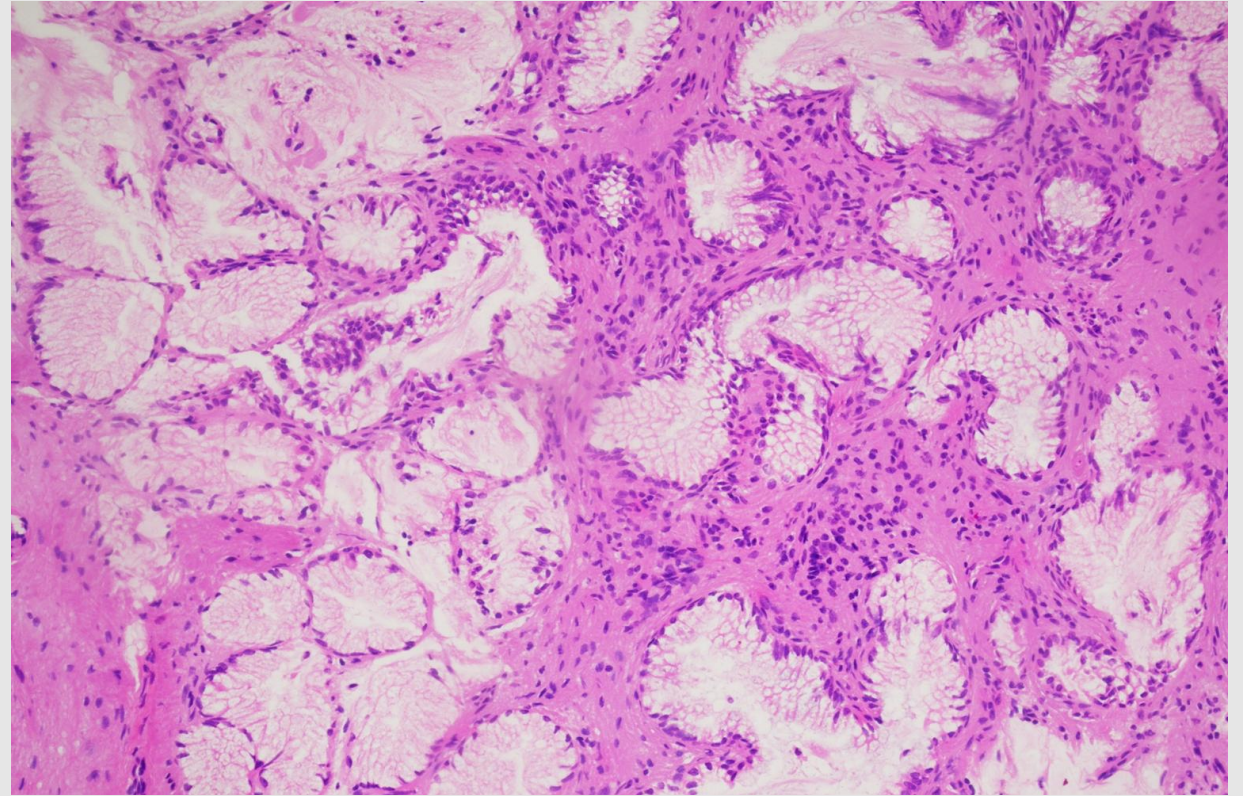
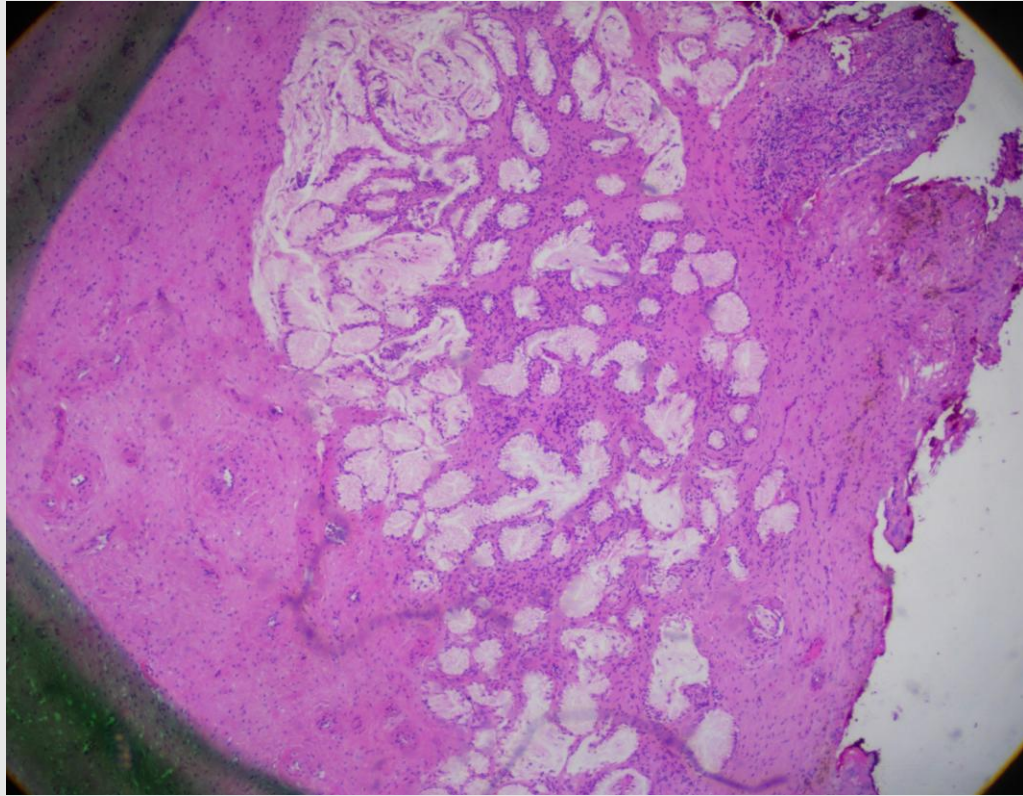
## Histological findings – expert review

- The expert opinion concluded that this represented an unusual form of **gastric metaplasia with intestinal differentiation** and, importantly, **was not considered premalignant**.
- **"The expert opinion also included a comment** noting that vaginal adenosis can sometimes exhibit gastric differentiation. Occasional prior cases have shown the coexistence of cervical gastric-type lesions and vaginal adenosis with gastric differentiation. Rarely, these lesions have been observed in association with Peutz-Jeghers syndrome."

## Cytology-Histology Discordance Timeline (2017–2025):

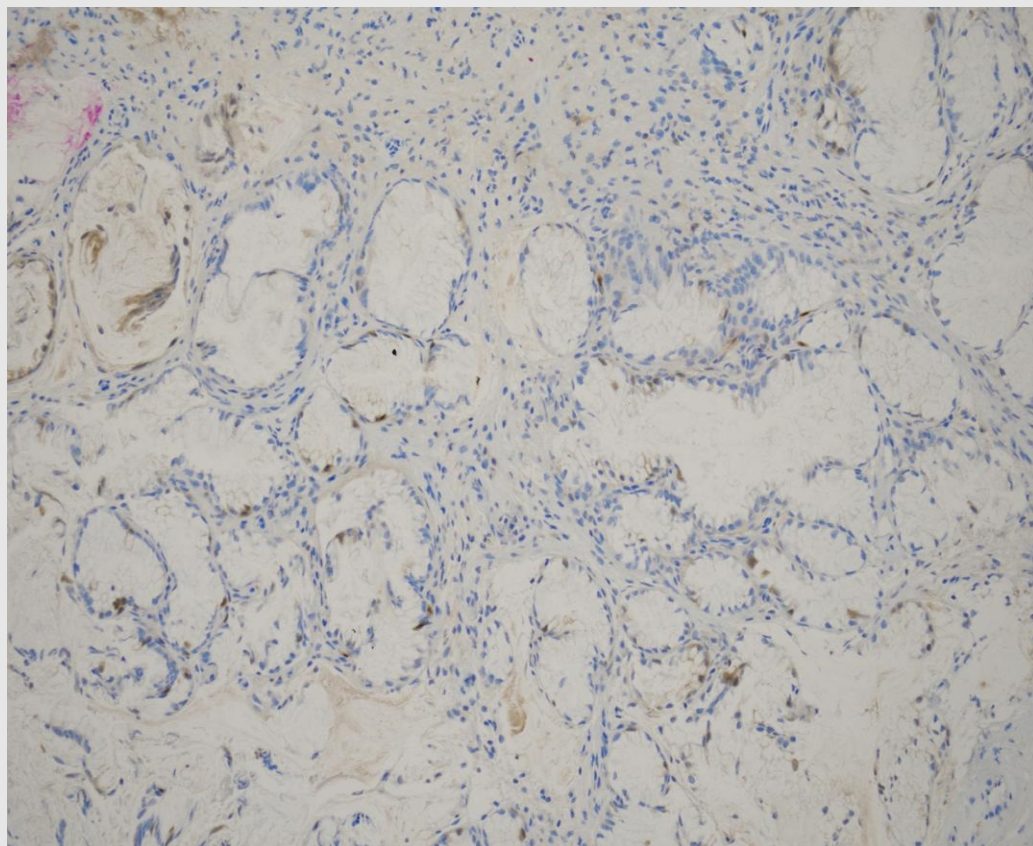
- Multiple instances of high-grade dyskaryosis on cervical cytology.
- Corresponding histology repeatedly showed only CIN I or HPV-related changes.
- No CIN II/III or invasive carcinoma identified.
- Multiple biopsies, loop excisions (LLETZ), and ultimately a hysterectomy failed to explain the persistent severe cytological abnormalities.
- Post-hysterectomy, vaginal vault cytology continued to show abnormal (high-grade) cells.



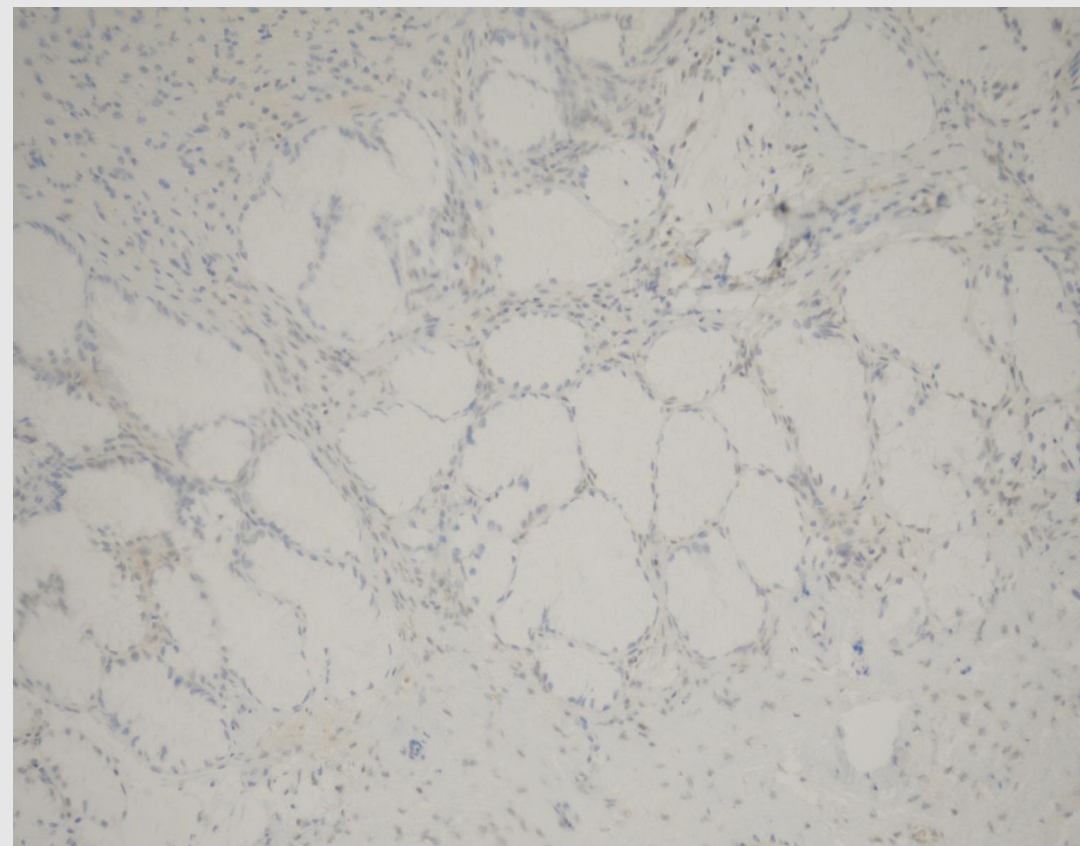


Hysterectomy specimen showed a focus of endocervical type mucinous glands showing bland cytological features at the anterolateral aspect of the cervix/proximal end of the vagina. These glands conform to a lobulated architecture with no evidence of infiltration.





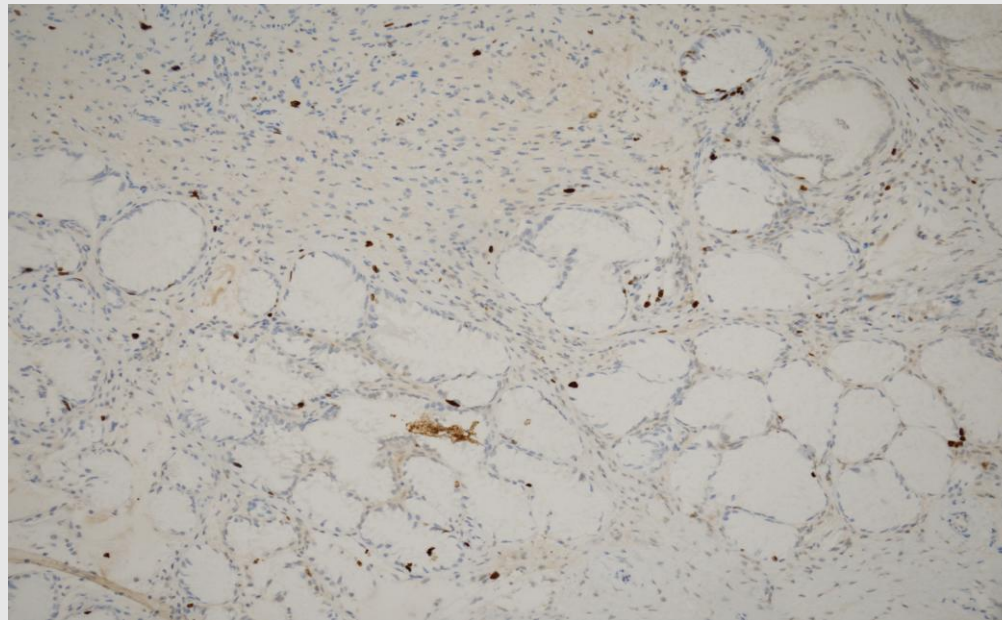
P16 negative



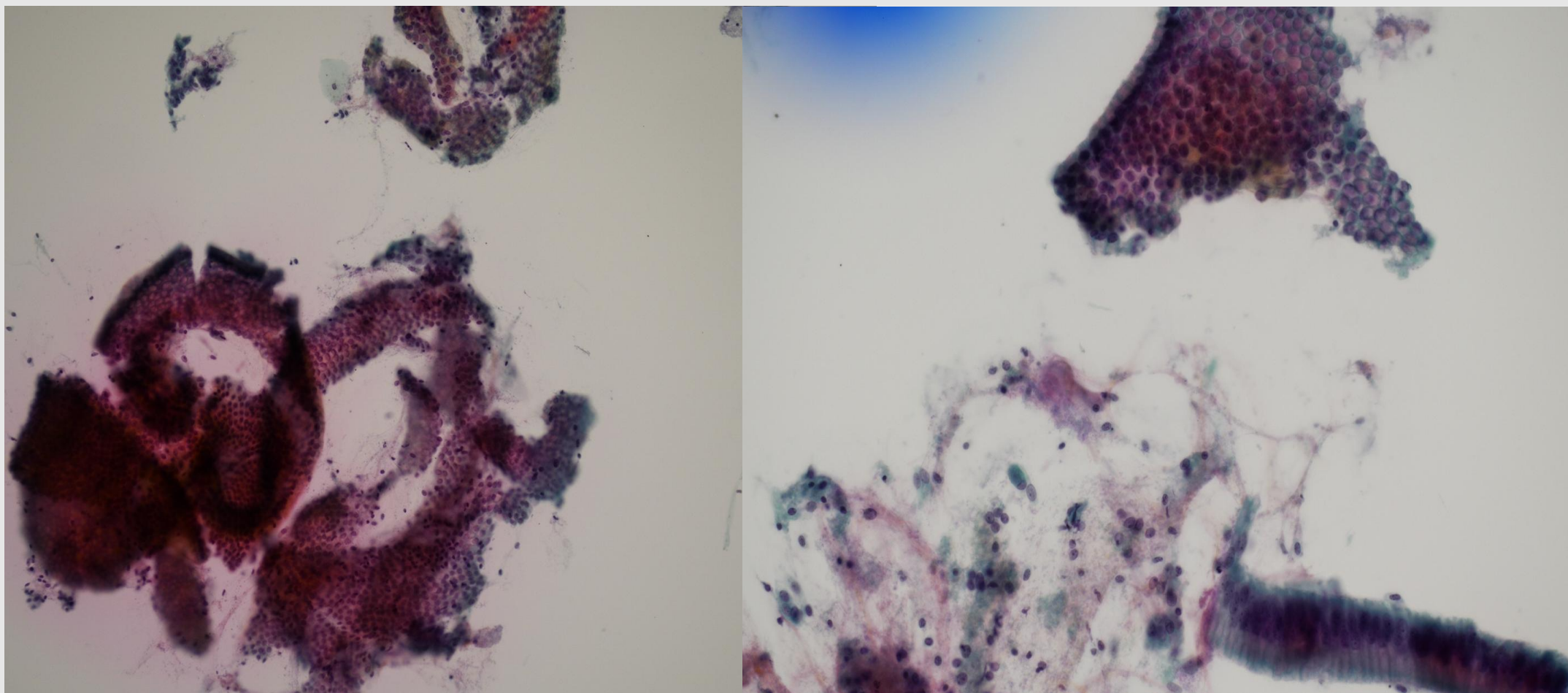
CEA negative



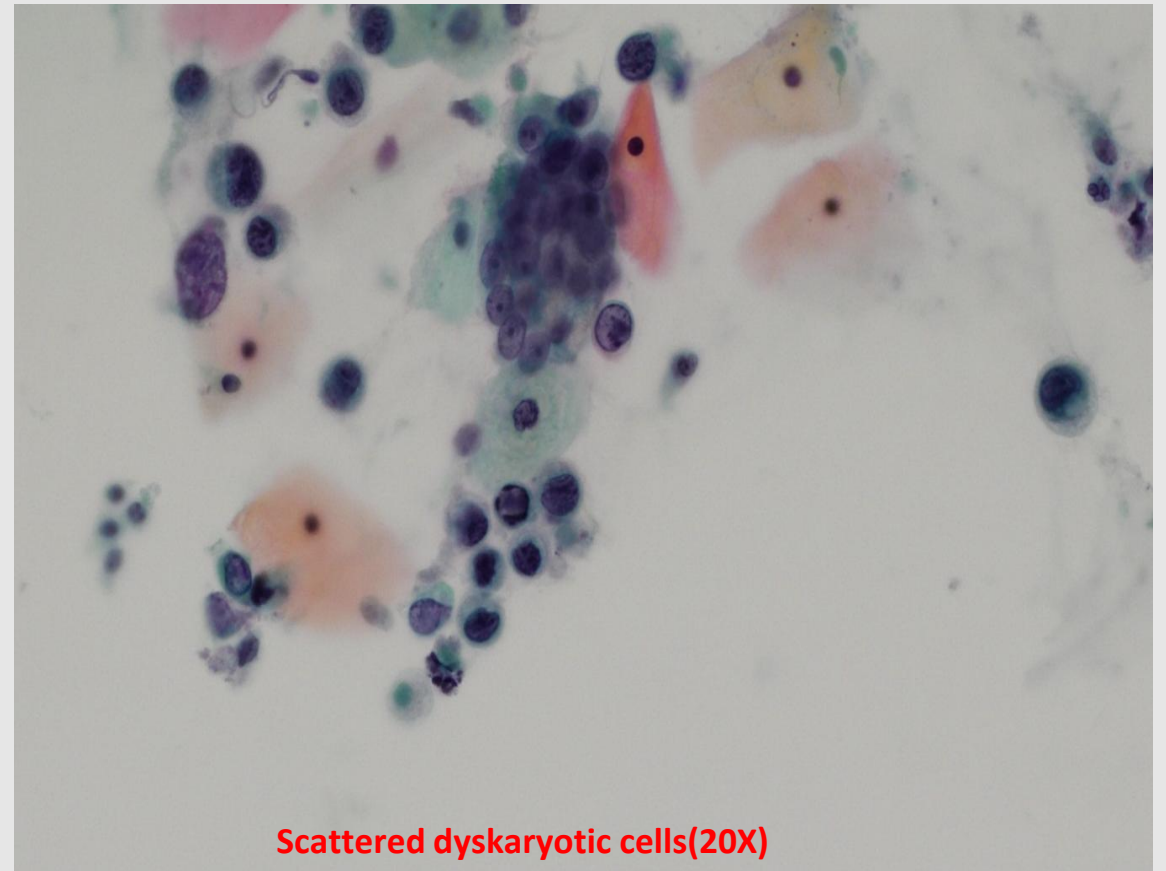
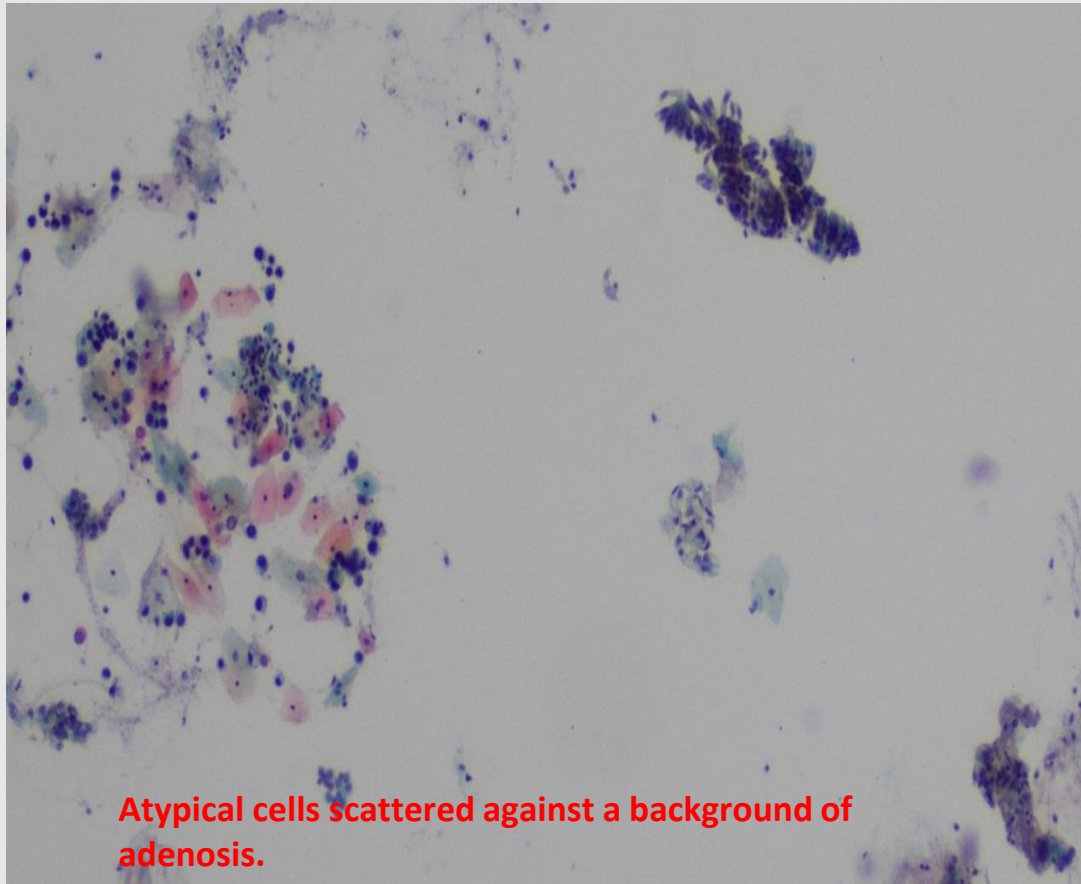
- On immunohistochemistry, the glandular epithelium is positive to AE1/3 and ER (focal), and negative to p16, mCEA, PAX8 and PR; p53 shows wild type expression and Ki67 proliferation index is low. The features are favoured to represent **vaginal adenosis**, which is keeping with the clinical impression/known history.
- The lack of an infiltrative growth and cytological atypia together with a negative CEA immunostaining do not support a diagnosis of endocervical adenocarcinoma.



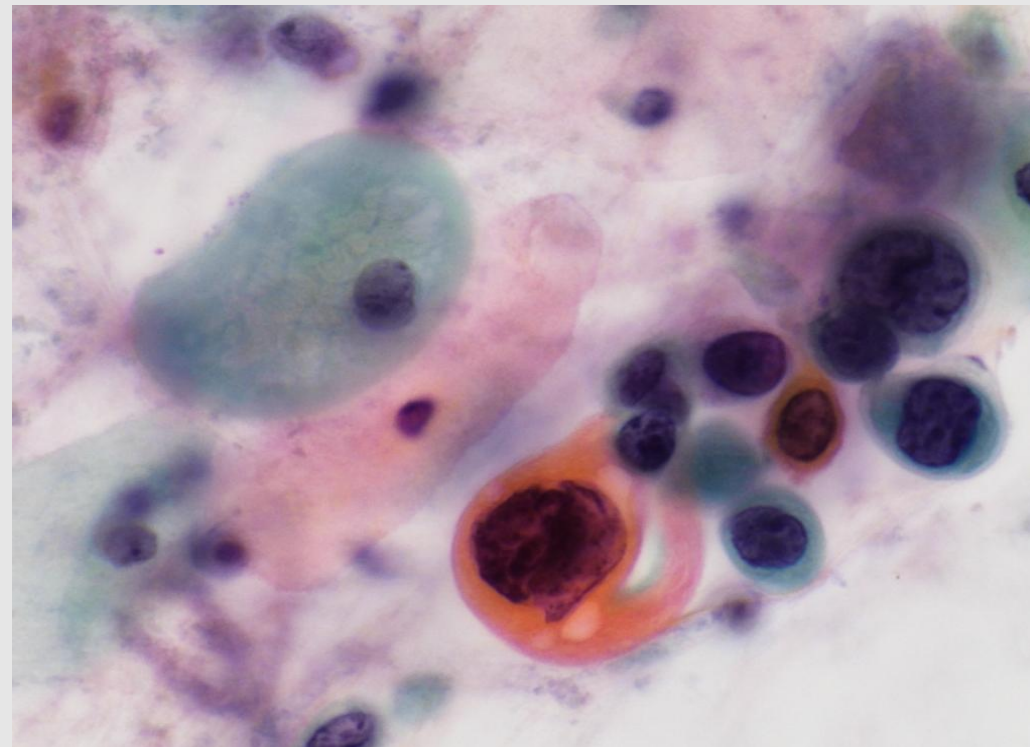
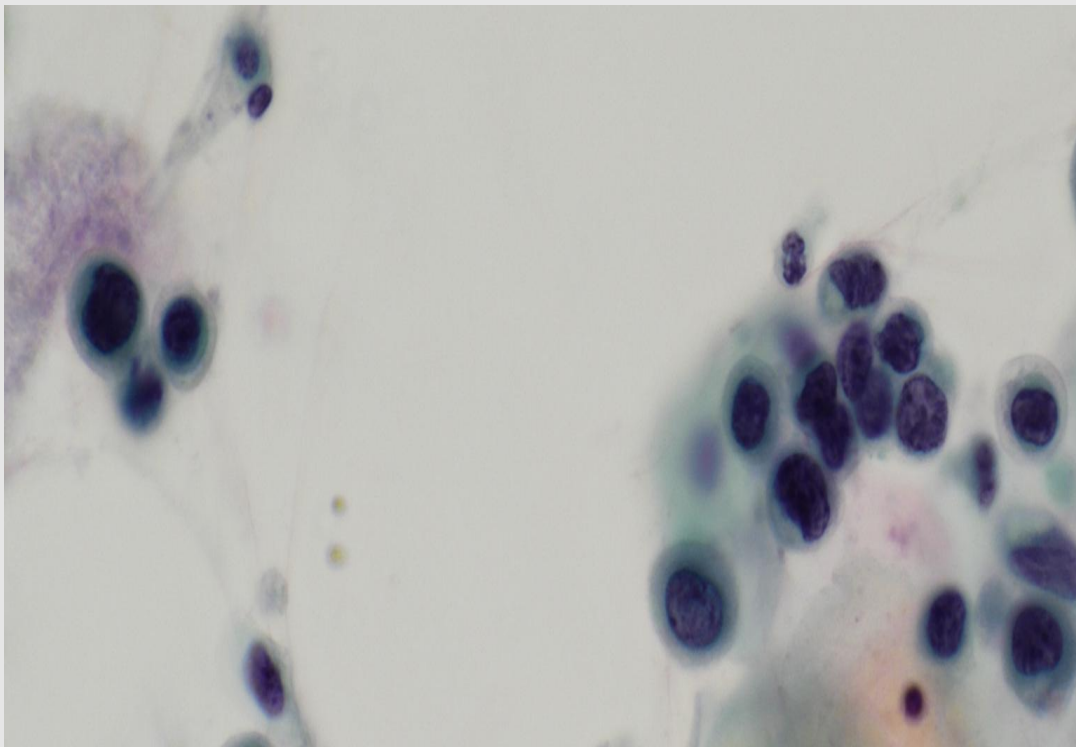
Ki67proliferation index is low



This is a vaginal vault smear showing features of adenosis

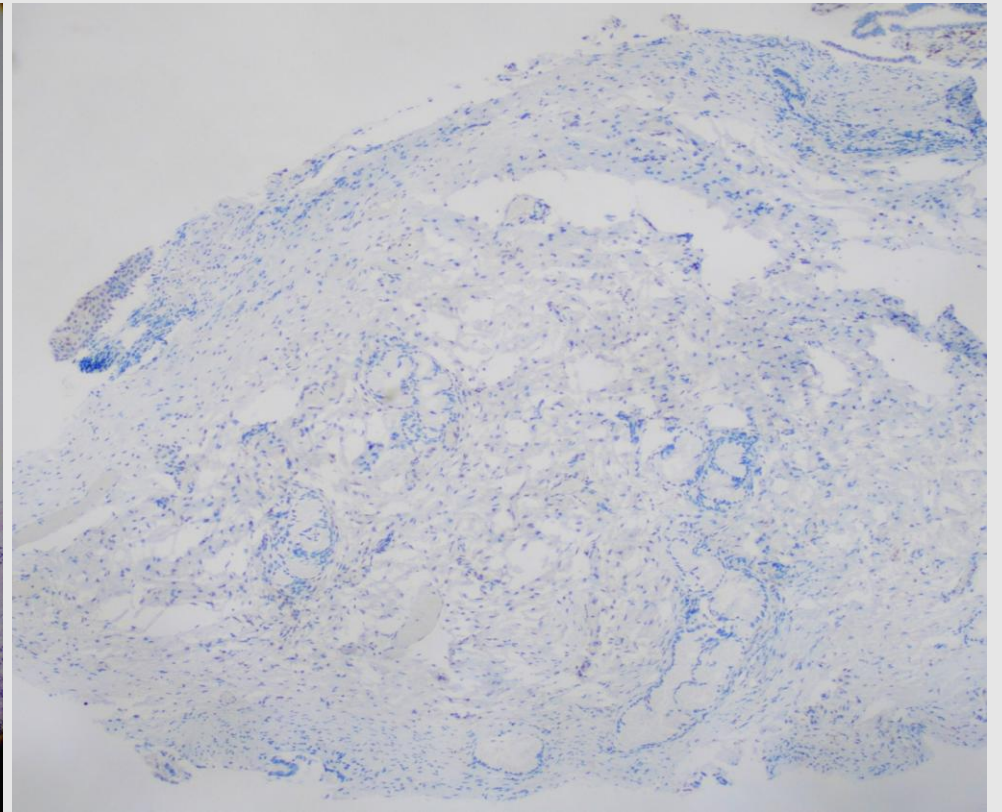
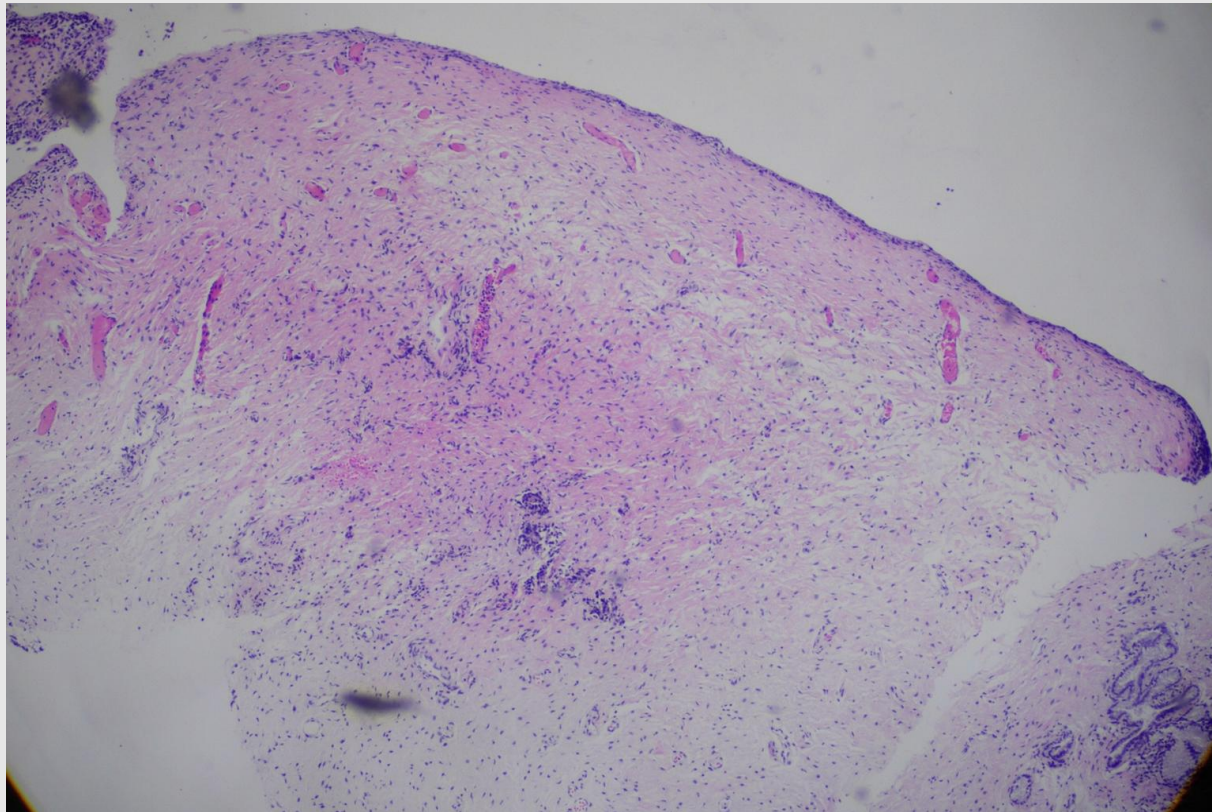






High grade dyskaryosis(severe)





**The most recent vaginal vault biopsy showed extensive surface epithelial erosion, and was deemed inadequate for assessment of squamous abnormality. Immunohistochemical staining for p16 was negative.**

# Discussion

## DES Exposure and Glandular Abnormalities:

- This case demonstrates persistent **vaginal adenosis** and an **unusual cervical gastric metaplasia** with intestinal features.
- This finding is rare but documented in DES-exposed individuals. Their correct identification is essential to avoid overdiagnosis and unnecessary treatment. Expert histopathological review proved pivotal in establishing a benign diagnosis.

## Persistent Cytology-Histology Discordance:

- The long-standing presence of high-grade dyskaryosis on cytology, without histological confirmation of CIN II/III or malignancy, posed a significant diagnostic dilemma.
- While low-grade HPV-related changes and CIN I were observed, they did not account for the recurrent severe cytological abnormalities.
- The persistence of abnormal vault cytology following hysterectomy underscores the importance of an ongoing, cautious approach—balancing vigilance with the avoidance of overtreatment.
- This case illustrates the crucial role of **multidisciplinary team (MDT)** review in navigating persistent discordant findings.

## Future Management:

- The patient remains under close follow-up.
- A repeat vaginal vault cytology is planned in six months.
- Should the abnormal cytology persist, our department intends to prepare a **cell block** and apply additional immunohistochemical markers to better determine the origin of the atypical cells. This may help resolve the remaining diagnostic uncertainty.

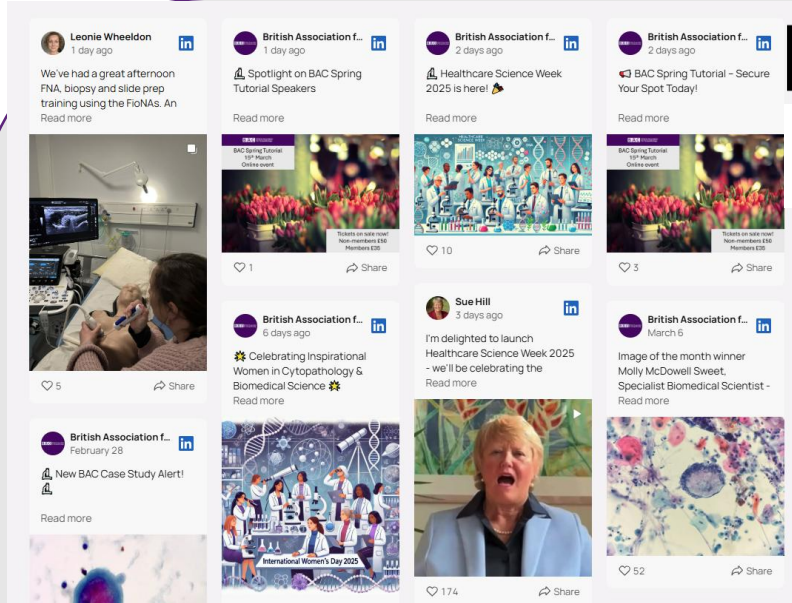
## Conclusion:

- This case exemplifies two intertwined challenges: the interpretation of benign yet unusual glandular changes in the context of probable DES exposure, and the management of persistent high-grade cytology in the absence of definitive high grade histological disease.
- It underscores the value of expert pathological review, multidisciplinary oversight, and personalised patient-centered follow-up in navigating complex gynaecological cases.

# References

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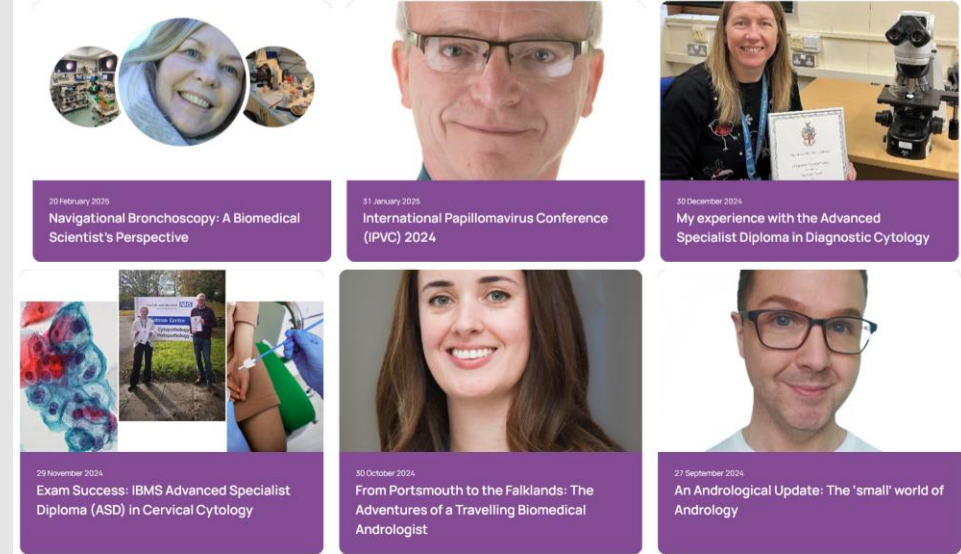




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