

Case Report

- A 66-year-old woman was referred to the Urology Clinic following the identification of a 2.5 x 2.3 x 2.0 cm left mid-pole renal mass on imaging. The patient had a history of gross hematuria a few months prior.
- Initial diagnostic work-up, including cystoscopy and urine cytology, yielded no abnormalities. MRI abdomen described a 2.9 x 2.6 x 2.3 cm mass in the mid-pole of the left kidney felt to represent renal cell carcinoma, less likely urothelial carcinoma. There was no regional adenopathy at that time. Subsequent CT scan identified again the above-mentioned infiltrative, solid, enhancing renal mass in conjunction with multifocal retroperitoneal and iliac chain lymphadenopathy. An interventional radiology-guided retroperitoneal lymph node (RPLN) biopsy was obtained.
- Histologic examination of the RPLN biopsy revealed sheets and cords of relatively monomorphic cells containing variable amounts of intracytoplasmic mucin and areas of focal glandular lumina formation.
- Immunohistochemical stains for PAX-8, CK7, CK20, GATA-3, p63/CK903 (double stain), p16INK, and e-cadherin were performed. The neoplastic cells demonstrated strong and diffuse positivity for CK7 and p16INK, moderate diffuse positivity for CK903, weak focal positivity for GATA-3, and retained e-cadherin immunoreactivity. They were negative for PAX-8, p63, and CK20. High-risk Human Papillomavirus (HPV) E6/E7 mRNA In Situ Hybridization (ISH) testing was performed and yielded positive results, supporting the diagnosis of an HPV-associated carcinoma.

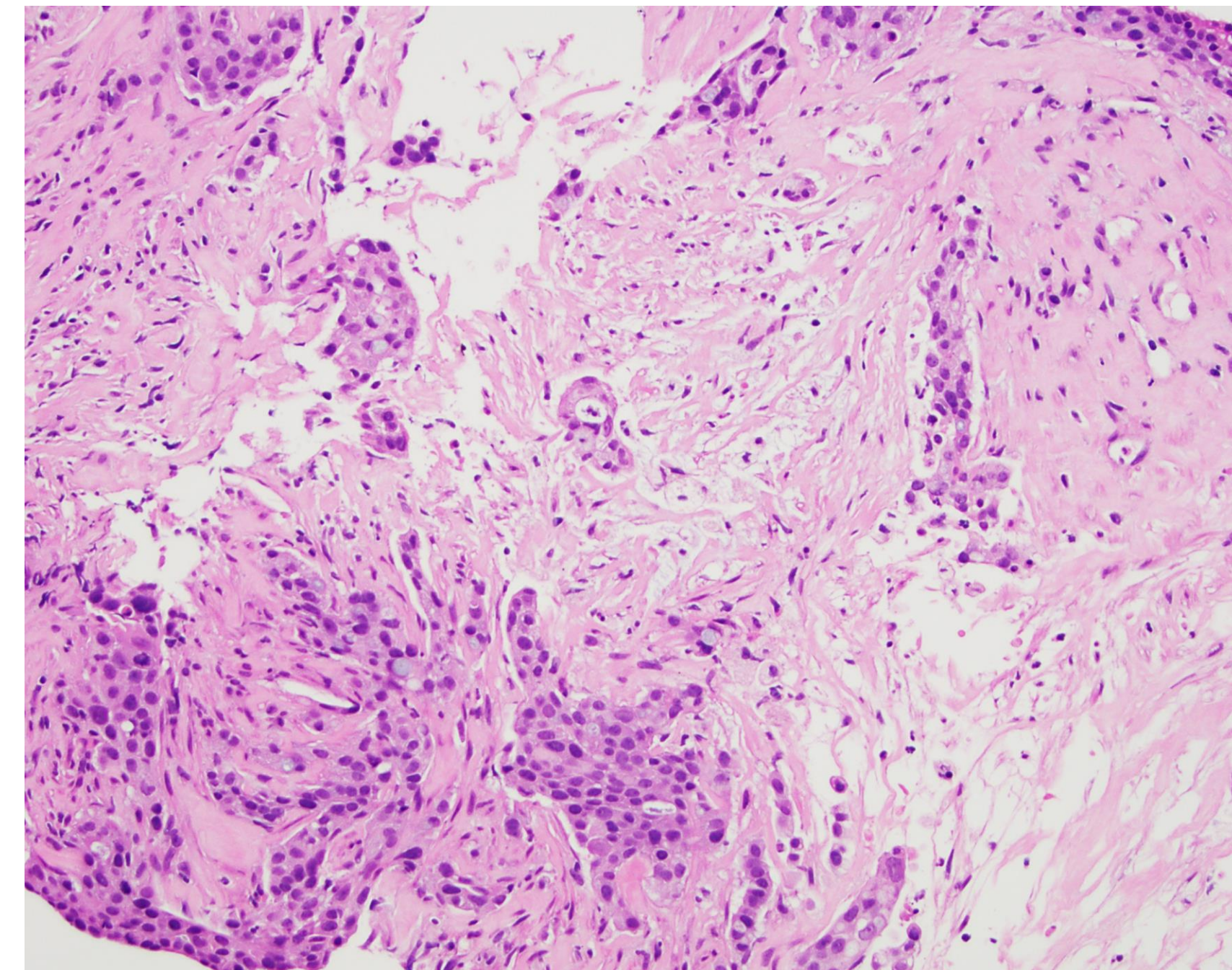


Figure 1. Metastatic ISMC to RPLN. (H&E, 200x)

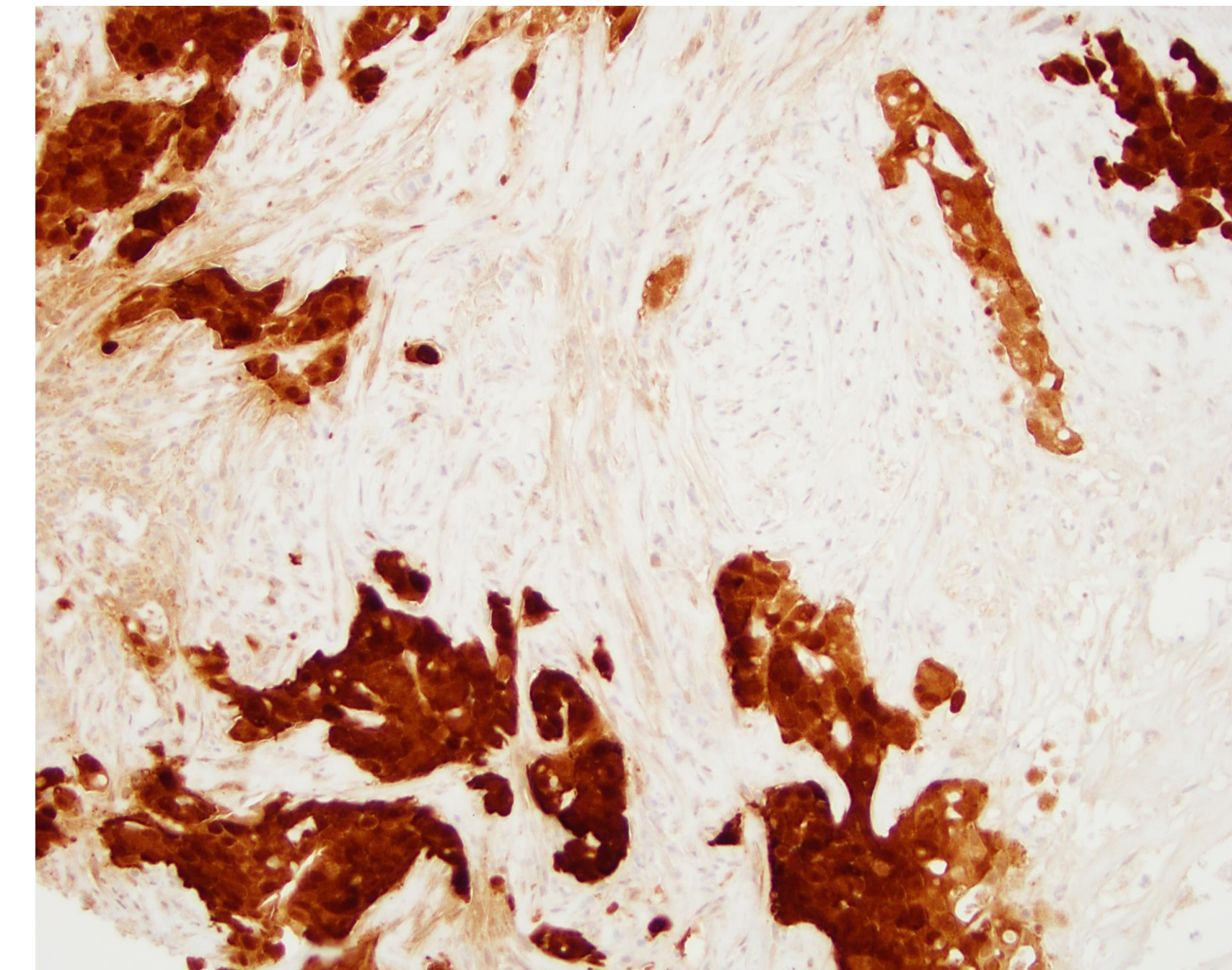


Figure 2. Neoplastic cells show strong and diffuse positivity for P16 immunostain. (p16 IHC, 200x)

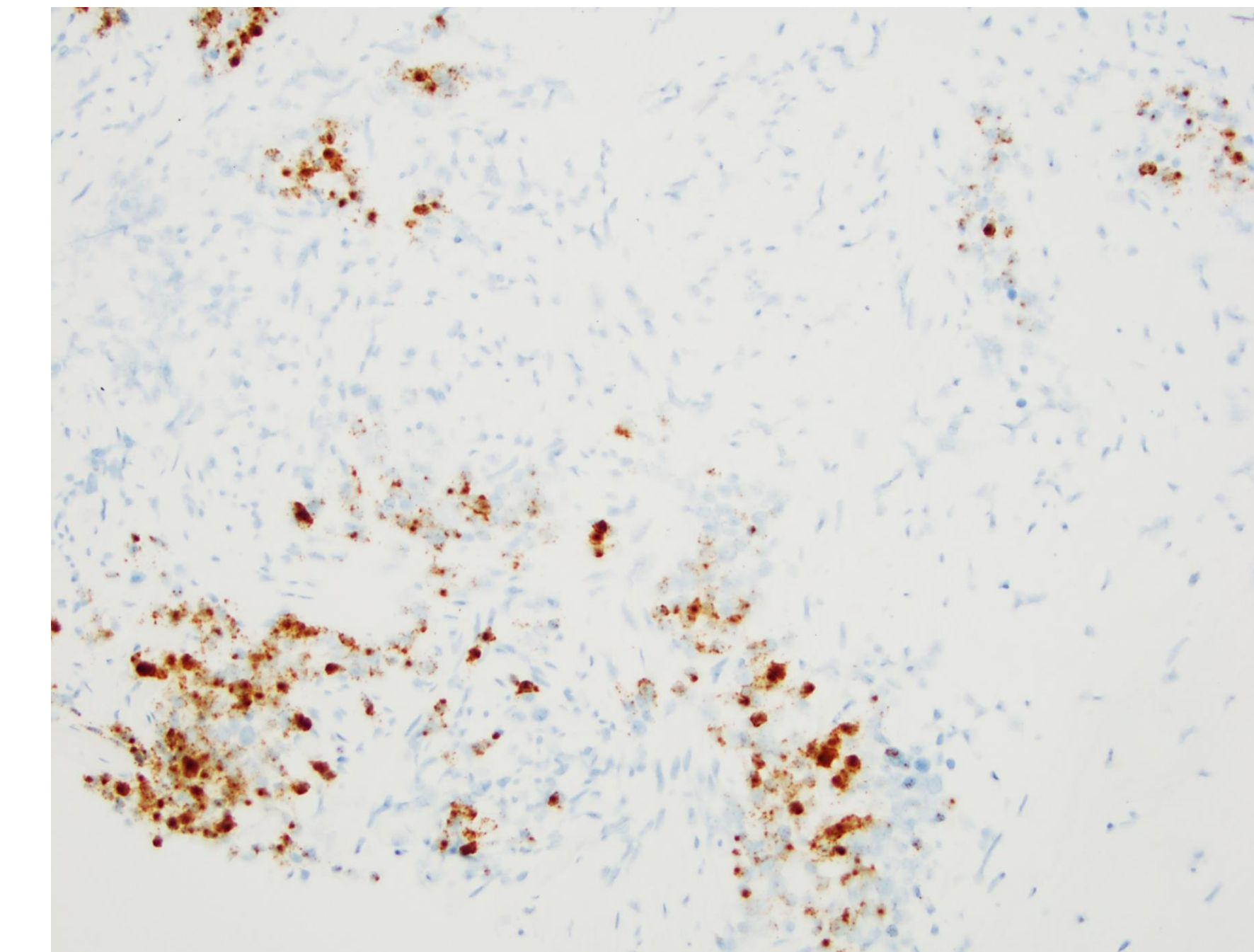


Figure 3. HPV ISH positive tumor cells (HPV E6/E7 mRNA ISH, 200x)

- These findings, combined with the patient's clinical profile, argued against a renal primary and raised suspicion for a metastatic malignancy of possible uterine cervix or lower gynecological tract origin. The patient was thus referred to the gynecological evaluation.
- Upon gynecologic examination, the ectocervix was noted to be replaced by a friable exophytic nodular mass.
- Cervical biopsy exhibited similar morphology and immunohistochemical profile as the prior RPLN biopsy.
- These findings ultimately led to a diagnosis of stage IV invasive carcinoma, HPV-associated, of the cervix, with morphology suggestive of invasive stratified mucin-producing carcinoma (ISMC), which is considered a variant of HPV-associated cervical adenocarcinoma.

Key Diagnostic Points

- The presence of a renal mass with retroperitoneal lymph node involvement typically raises suspicion for a primary kidney malignancy; however, findings of diffuse, including iliac, adenopathy and unusual morphologic appearance warrant investigation of a possible non-renal origin.
- ISMC is believed to originate from HPV-infected reserve cells within the cervical transformation zone that retain multipotential differentiation abilities, possibly fueling the tumor's aggressive behavior, including nodal and distal metastasis, recurrence, and resistance to chemoradiation [1, 2].
- This case underscores the importance of careful clinicopathological correlation in atypical presentations to ensure accurate diagnosis and appropriate treatment planning.

References

1. Stolnicu S, Segura S, Parra-Herran C, Horn LC, Hoang L, Terinte C, Pesci A, Aviel-Ronen S, Kyokawa T, Alvarado-Cabrero I, Oliva E, Soslow RA, Park KJ. Invasive Stratified Mucin-producing Carcinoma (ISMC) of the Cervix: A Study on Morphologic Diversity. *Am J Surg Pathol.* 2020 Jul; PMID: 32235154; PMCID: PMC7289664.
2. Stolnicu S, Hoang L, Zhou Q, Iasonos A, Terinte C, Pesci A, Aviel-Ronen S, Kiyokawa T, Alvarado-Cabrero I, Oliva E, Park KJ, Soslow RA. Cervical Adenosquamous Carcinoma: Detailed Analysis of Morphology, Immunohistochemical Profile, and Outcome in 59 Cases. *Int J Gynecol Pathol.* 2023 May 1; Epub 2022 Aug 31. PMID: 36044310; PMCID: PMC9971353.