EXPERIMENTAL ONCOLOGY

https://doi.org/10.15407/exp-oncology.2026.02.172

O. Kovalyov [1, *], S. Zavhorodniy [1], O. Tolok [2], A. Anenko [2], M. Kubrak [1], M. Danilyuk [1], K. Kovalyov [1]

[1] Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine
[2] YULIS Medical Oncology Center, Zaporizhzhia, Ukraine

* Correspondence: E-mail: kovalev.onco@gmail.com

PHENOTYPIC SHIFT OF ADENOCARCINOMA TO SQUAMOUS CELL CARCINOMA OF RECTUM AFTER NEOADJUVANT CHEMORADIOTHERAPY WITH DETECTION OF HPV16: A CLINICAL CASE

Adenosquamous carcinoma and pure squamous cell carcinoma (SCC) of the rectum are extremely rare malignancies, accounting for approximately 0.15% of all colorectal cancers. Increasing attention has been paid to tumor phenotypic plasticity in the context of intensive anticancer therapy. We report the case of a 45-year-old patient with locally advanced rectal adenocarcinoma (cT4bN2M0) who underwent total neoadjuvant therapy consisting of XELOX chemotherapy combined with pelvic radiotherapy. Baseline biopsy samples from multiple tumor areas showed moderately differentiated adenocarcinoma with an intestinal immunophenotype. After treatment, the resected tumor showed complete loss of intestinal differentiation markers (CK20, CDX2) and the emergence of a squamous immunophenotype with positive expression of p40 and p63. Histologically, the tumor was composed exclusively of poorly differentiated SCC. PCR analysis detected HPV16 DNA in the SCC component. Strong, diffuse $p16^{INK4a}$ expression was observed in both the primary adenocarcinoma and the post-treatment tumor. These findings indicate a marked therapy-associated phenotypic shift in tumor differentiation. However, the underlying biological mechanism remains uncertain. Possible explanations include therapy-associated tumor plasticity, clonal selection of a pre-existing squamous subclone, or an initially unrecognized mixed tumor phenotype. This case highlights the importance of careful pathological reassessment after neoadjuvant therapy in rectal cancer and illustrates the complexity of interpreting phenotypic changes in treated tumors. The potential role of HPV in such processes remains hypothetical and requires further investigation.

Keywords: rectal adenocarcinoma, squamous transdifferentiation, HPV16, neoadjuvant chemoradiotherapy.

Rectal cancer is predominantly represented by adenocarcinoma (AC), arising from the glandular cuboidal epithelium. Mixed adenosquamous carcinoma (ASC) or primary squamous cell carcinoma (SCC) accounts for approximately 0.15% of all colorectal malignancies [1, 2]. An even rarer phenomenon is the emergence of a squamous phenotype in tumors initially diagnosed as AC, either during tumor progression or after anticancer therapy.

Although phenotypic plasticity is a fundamental characteristic of malignant cells, the underlying biological mechanisms remain poorly understood [3, 4].

Citation: Kovalyov O, Zavhorodniy S, Tolok O, Anenko A, Kubrak M, Danilyuk M, Kovalyov K. Phenotypic shift of adenocarcinoma to squamous cell carcinoma of the rectum after neoadjuvant chemoradiotherapy with detection of HPV16: A clinical case. *Exp Oncol.* 2026; 48(2): 172-180. https://doi.org/10.15407/exp-oncology.2026.02.172

The literature contains reports describing phenotypic shifts of cancer cells occurring during antitumor therapy [5]. In several tumor types, including cancers of the esophagus, lung, and head and neck region, therapy-associated changes toward squamous differentiation have been reported [6, 7]. Rare cases of histological changes of colorectal AC into other aggressive phenotypes, including choriocarcinoma, following chemotherapy, have also been described [8].

Total neoadjuvant therapy (TNT), combining radiotherapy and systemic chemotherapy, is currently the standard treatment approach for locally advanced rectal cancer. This strategy improves local disease control, pathological complete response rates, and overall survival [9].

However, TNT is associated with adverse effects resulting from damage not only to tumor cells but also to normal tissues, thereby increasing treatment-related toxicity. At the molecular level, intensive irradiation, combined with cytotoxic therapy, induces profound biological stress, including DNA damage, epigenetic remodeling, immune modulation, and clonal selection [10, 11]. These processes may contribute to tumor plasticity and shifts in the dominant tumor phenotype.

The role of human papillomavirus (HPV) in the development of gastrointestinal AC remains controversial [12, 13]. Of particular interest is the potential contribution of oncogenic viruses to cellular phenotypic changes, possibly acting as co-factors in carcinogenesis [14].

In this article, we report a case of a woman with rectal AC that, after total neoadjuvant chemoradiotherapy, demonstrated a marked shift in tumor phenotype toward pure SCC, with detection of HPV type 16 in the post-treatment tumor tissue.

This case raises important questions regarding therapy-associated tumor plasticity, clonal selection, and the possible involvement of HPV in epithelial lineage changes under treatment-induced selective pressure.

Case presentation

In a 45-year-old woman, locally advanced rectal cancer staged as cT4bN2M0 was diagnosed in July 2024, based on clinical, radiological, and histopathological evaluation.

The tumor originated above the dentate line and anorectal junction and was located predominantly in the mid-rectum. The distal tumor margin was approximately 5 cm from the anal verge, with a longitudinal extent of about 10 cm (proximal margin ~15 cm from the anal verge), corresponding to a mid-to-low rectal tumor with predominant involvement of the mid-rectal segment. There was no involvement of the anal canal or the anorectal transitional zone.

Baseline biopsy samples obtained from five different tumor areas confirmed the moderately differentiated AC. Given the locally advanced nature of the disease, TNT was initiated, consisting of 4 cycles of XELOX chemotherapy combined with pelvic radiotherapy at a total dose of 40 + 20 Gy. Treatment was completed in March 2025.

No objective clinical response to TNT was observed, as tumor dimensions remained unchanged. However, radiotherapy was complicated by severe local toxicity, including radiation proctitis and the development of a pararectal abscess. Following surgical drainage and sanitation, a prolonged period of delayed wound healing and persistent inflammatory changes in the perineal region was noted. Due to these complications, definitive surgical treatment was postponed.

Subsequently, 5 months after completion of TNT and 11 months after the initial diagnosis, the patient underwent forced salvage surgery. Cytoreductive abdominoperineal extralevator excision of the rectum according to Holm was performed, together with hysterectomy with bilateral adnexectomy and resection of the posterior vaginal wall (en bloc AD resection), as well as D2 lymph node dissection.

The surgical specimen (pathology report No. 13790/25) consisted of 21 histological blocks (21 slides). Gross examination and sampling were performed according to the College of American Pathologists (CAP) protocol for colorectal AC, which focuses on TNM staging and does not require complete tumor bed mapping in routine practice.

The sampled blocks included the primary tumor areas, resection margins, mesorectal tissue, adjacent organs (vaginal wall, cervix, adnexa), stoma site, regional lymph nodes, and clinically suspected metastatic sites.

A total of 11 regional lymph nodes were examined, all of which were negative for metastatic involvement (ypN0, 0/11). The lymph nodes were small and preserved in architecture, with no evidence of metastases or therapy-induced regression changes (such as fibrosis, necrosis, or mucin pools).

Postoperatively, the patient received additional systemic chemotherapy with carboplatin + paclitaxel (3 cycles) and cisplatin + 5-fluorouracil (2 cycles), which proved ineffective. Despite multimodal treatment, rapid disease progression occurred, manifested by local recurrence and peritoneal metastases.

Histopathological examination demonstrated a lack of tumor response to therapy, corresponding to grade III therapeutic pathomorphosis according to the Ryan classification. The residual tumor was composed exclusively of poorly differentiated SCC with strong $p16^{INK4a}$ expression. Despite thorough morphological examination of the entire surgical specimen, no glandular structures or residual AC components were identified.

Given the marked morphological differences observed at various stages of tumor progression, additional immunohistochemical (IHC) and molecular analyses were performed on all archived tumor material, including assessment of HPV involvement.

The following markers were evaluated: cytokeratin 7 (DAKO, clone OV-TL 12/30), cytokeratin 20 (DAKO, clone Ks 20.8), cytokeratin 5/6 (DAKO, clone D5/16 B4), CDX-2 (DAKO, clone DAK-CDX2), p40 (Diagnostic BioSystems, polyclonal), p63 (Diagnostic BioSystems, clone DBR 16.1), $p16^{INK4a}$, (clone JC2), HPV16 (capsid protein L1, clone CAMVIR-1), E-cadherin (Diagnostic BioSystems, clone SPM471), vimentin (DAKO, clone V9), and mismatch repair proteins for MSI assessment (MLH-1 clone G168-15, MSH6 clone 44, PMS2 clone A16-4, and MSH2 clone FE11).

IHC evaluation was performed using a semi-quantitative approach, taking into account the type of staining, expression pattern, staining intensity, and the percentage of positive tumor cells.

For p16, only block-type staining was considered positive, defined as strong, diffuse nuclear and cytoplasmic expression in ≥70% of tumor cells. Focal or heterogeneous staining involving <70% of cells was considered non–block-type and interpreted as negative or non-specific.

For p63 and p40, nuclear staining was evaluated. Expression was categorized based on the proportion of positive tumor cells (<10% negative, 10%—50% focal, >50% diffuse for p63; <5%—10% negative, ≥10% positive for p40). The diffuse nuclear expression of p63 and p40 was interpreted as supporting squamous differentiation.

Staining intensity for all markers was graded as 0 (absent), 1+ (weak), 2+ (moderate), or 3+ (strong).

IHC findings were interpreted in the context of tumor morphology and clinical data. p16 expression was interpreted with caution, as it is not specific for HPV-driven carcinogenesis in the absence of molecular confirmation.

HPV DNA status was assessed by PCR analysis of vaginal swab specimens as well as tumor tissue from SCC components using an IVD-certified test system (Seegene, South Korea) and a CFX96 real-time thermocycler (Bio-Rad, USA), with a sensitivity of

Immunohistochemical and molecular profile of the tumor at different stages of evolution

Marker	Primary tumor (AC)	Residual tumor after TNT (SCC)	Metastasis (SCC)
Hematoxylin & eosin staining	Glandular architecture, adenocarcinoma morphology	Squamous cell morphology	Squamous cell morphology
CK20	+	—	—
CDX2	+	—	—
p40	—	+	+
p63	Not performed	+	+
$p16^{INK4a}$	+	+	+
Capsid protein L1	Not performed	—	—
E-cadherin	+	+	Not performed
Vimentin	—	—	Not performed
MSI	Microsatellite stable	Microsatellite stable	Microsatellite stable
HPV16 DNA in the tumor	Not performed	+	Not performed
HPV DNA in the vaginal swab	Not performed	—	—

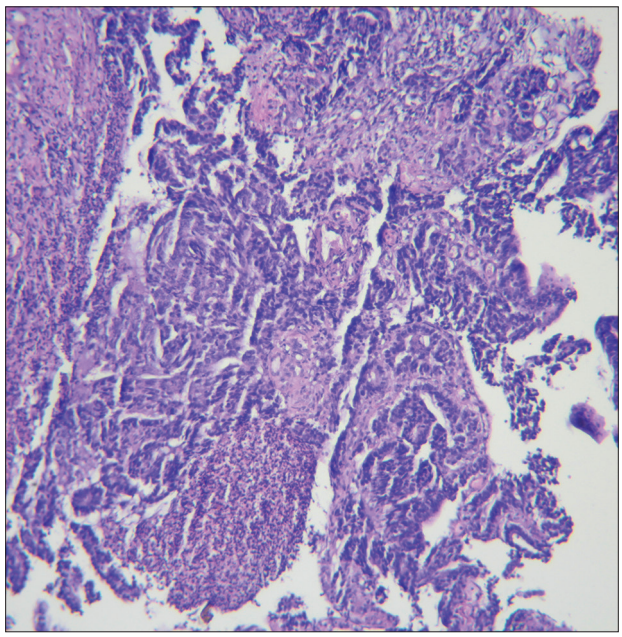

Fig. 1. Rectal adenocarcinoma (cT4bN2M0) before treatment. Hematoxylin and eosin staining, ×200

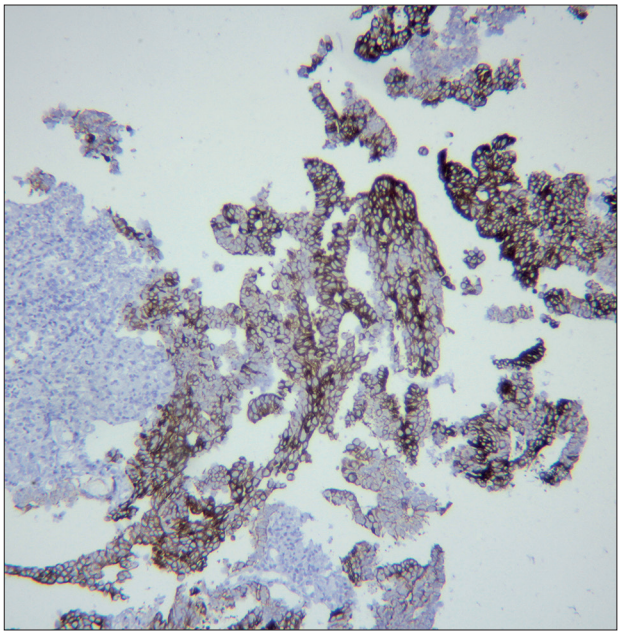

Fig. 2. Rectal adenocarcinoma (cT4bN2M0) before treatment. Diffuse cytoplasmic expression of cytokeratin 20 (CK20) (DAKO, clone Ks 20.8), ×200

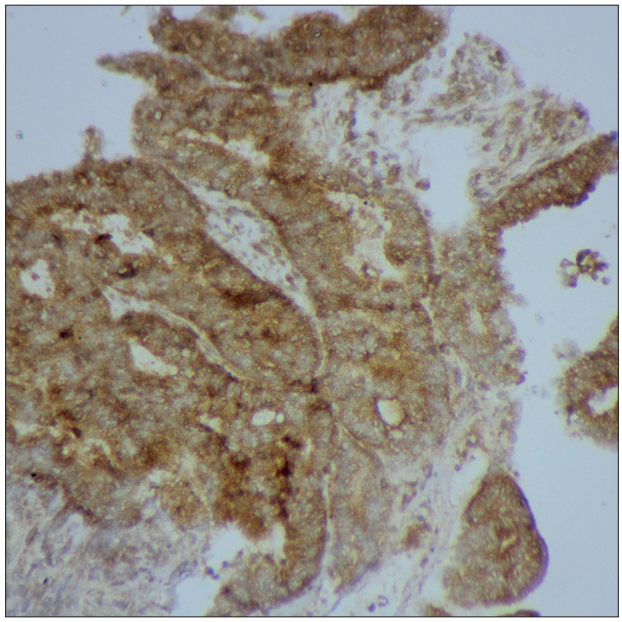

Fig. 3. Rectal adenocarcinoma (cT4bN2M0) before treatment. Strong diffuse nuclear and cytoplasmic expression of $p16^{INK4a}$ (clone JC2), ×200

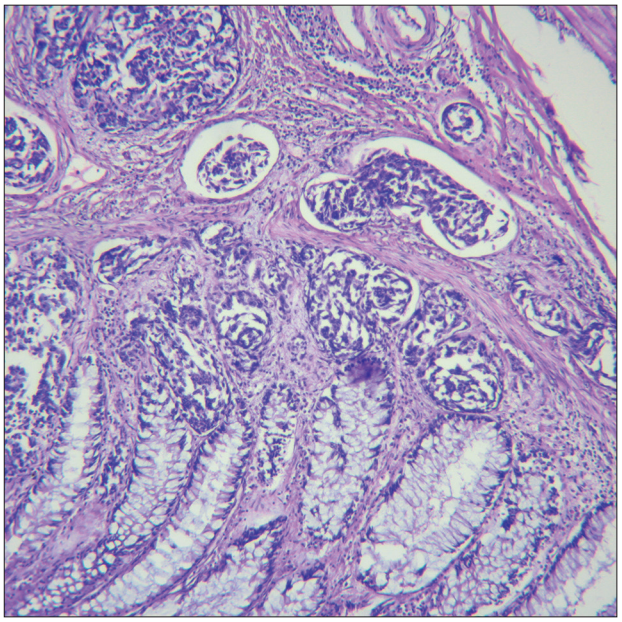

Fig. 4. Squamous cell carcinoma of the rectum in the same patient after total neoadjuvant therapy. Hematoxylin and eosin staining, ×200

50 copies per reaction. HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 66, 68, 69, 70, 73, and 82 were analyzed.

The obtained results are summarized in the Table. Histopathological and IHC features are shown in Figs 1—6.

Due to the nature of the biopsy (core needle biopsy), only tumor tissue was available, and no adjacent normal mucosa was present to serve as an internal positive control.

IHC staining quality was verified using appropriate external positive controls in accordance with standard laboratory protocols.

In our case, the IHC profile of the primary tumor was consistent with rectal adenocarcinoma with typical intestinal differentiation, demonstra-

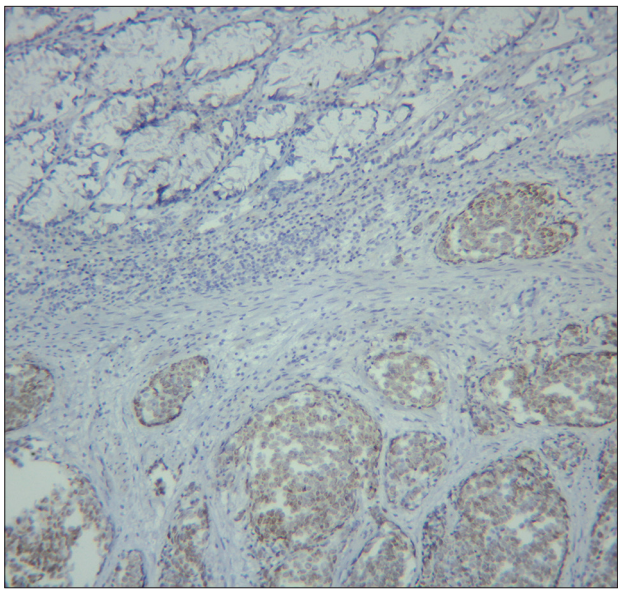

Fig. 5. Post-therapy rectal squamous cell carcinoma. Positive nuclear expression of p40 (Diagnostic BioSystems, polyclonal), ×200

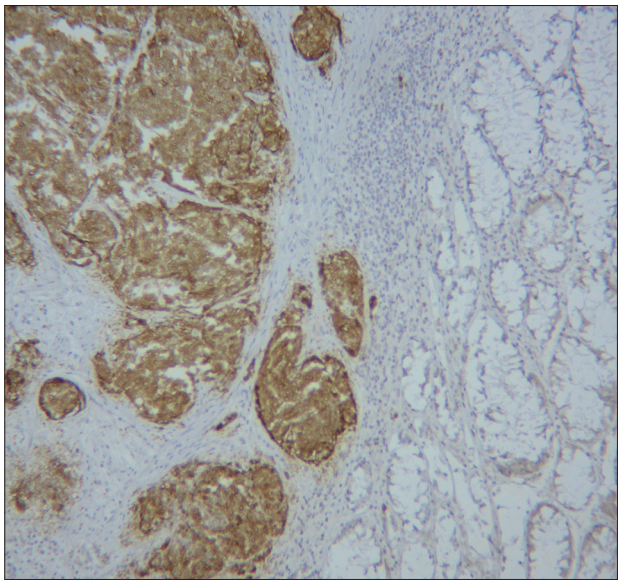

Fig. 6. Post-therapy rectal squamous cell carcinoma. Diffuse overexpression of $p16^{INK4a}$ (clone JC2), ×200

ted by positive expression of CK20 and CDX2 and the absence of squamous marker p40.

In tumor tissue obtained after TNT, loss of intestinal differentiation markers was observed ($CK20^{-}$, $CDX2^{-}$), accompanied by the emergence of a distinct squamous immunophenotype with positive expression of p40 and p63, consistent with SCC morphology.

E-cadherin expression was preserved, while vimentin expression was absent in all examined tumor specimens.

Notably, the primary AC showed strong diffuse expression of $p16^{INK4a}$, which is uncommon for most colorectal adenocarcinomas. The tumor also showed persistent strong expression of $p16^{INK4a}$ after treatment. HPV16 DNA was identified only in the SCC components.

Microsatellite status remained stable (microsatellite stable, MSS) throughout all stages of tumor progression. No differences in mismatch repair protein expression were observed between pre-treatment and post-treatment samples.

NRAS mutation analysis was not performed, as it is not routinely recommended for primary rectal AC and would not have altered neoadjuvant treatment decisions. Likewise, *NRAS* testing is not standard in SCC, where RAS pathway alterations are uncommon, and its absence does not affect the interpretation of this case.

Extensive histopathological examination of the entire resection specimen revealed no residual glandular structures or mixed adenosquamous components.

A total of 21 histological blocks (21 slides) were examined from the tumor bed and surrounding tissues to exclude the presence of residual AC or mixed adenosquamous components.

Standard tumor regression grading (TRG) systems (e.g., the Ryan and Mandard systems) were considered; however, their application was limited in this case due to the marked change in tumor phenotype after neoadjuvant therapy.

No classical morphological features of regression (such as fibrosis, necrosis, or mucin pools) were identified in the tumor bed. Therefore, treatment response was assessed descriptively, based on the proportion of viable tumor tissue and the absence of histological signs of regression.

This limitation reflects the lack of established criteria for evaluating regression in cases with therapy-associated phenotypic shift.

Discussion

Rectal AC accounts for approximately 90% of malignant tumors of the rectum. Other histological types, including neuroendocrine tumors, lymphomas, gastrointestinal stromal tumors, and sarcomas, are distinctly uncommon. ASC is an exceptionally rare entity, accounting for approximately 0.15% of colorectal malignancies, while

pure SCC of the rectum remains a pathological rarity [15—17].

Histologically, ASC is defined by the coexistence of glandular and squamous components, each comprising at least 10%—20% of the tumor volume, according to the 2019 WHO Classification of Digestive System Tumours [18]. In contrast, pure rectal SCC without any glandular component has been reported only sporadically, with fewer than 150 documented cases over several decades and no standardized treatment recommendations [1].

Several pathogenetic hypotheses have been proposed to explain the presence of squamous differentiation in the rectum. One of them is based on squamous metaplasia of the rectal mucosa, in which chronic inflammation or carcinogenic stimuli induce transformation of columnar epithelium into squamous epithelium. This phenomenon has been described in inflammatory bowel disease and in association with HPV infection, with subsequent progression from metaplasia to dysplasia and carcinoma [19—21].

An alternative explanation involves the presence of multipotent basal or stem-like cells at the anorectal junction capable of divergent differentiation. Experimental data and histological evidence suggest that these cells may serve as a reservoir for squamous differentiation under inflammatory, viral, or therapeutic pressure [22].

Tumor phenotypic plasticity is increasingly recognized as a hallmark of cancer, particularly under strong genotoxic and inflammatory stress. Current data indicate that such plasticity is more frequently driven by epigenetic reprogramming rather than by the acquisition of new driver mutations [3, 23]. In this context, neoadjuvant chemoradiotherapy represents a potent selective force, inducing DNA damage, oxidative stress, immune modulation, and clonal selection [24].

Radiotherapy, in particular, promotes chronic inflammation and tissue remodeling, potentially favoring survival of tumor cell populations with enhanced resistance to hypoxia and DNA damage [25].

In some tumor types, squamous differentiation has been associated with altered responses to radiotherapy and chemotherapy, suggesting that lineage plasticity may influence tumor adaptation under therapeutic pressure [26].

In the present case, the marked change in tumor phenotype observed after neoadjuvant therapy raises the possibility of therapy-associated tumor plasticity. However, the precise biological mechanism underlying this shift cannot be definitively established in a single case report.

Several alternative explanations should be considered. One possibility is clonal selection of a pre-existing squamous subclone that was not detected in the initial biopsy samples due to limited tissue sampling. Another potential explanation is the presence of an initially mixed adenosquamous tumor in which the squamous component became dominant after treatment. Tumors arising in the anorectal transitional zone may exhibit complex patterns of epithelial differentiation, which can complicate interpretation of tumor lineage. In this context, the observed findings most likely reflect therapy-associated changes in the dominant tumor phenotype rather than definitive proof of transdifferentiation.

Several biological mechanisms may potentially contribute to the observed phenotypic shift. Intensive chemoradiotherapy represents a strong selective pressure capable of inducing epigenetic remodeling, clonal selection, and adaptive reprogramming of tumor cells. Experimental and clinical studies increasingly suggest that therapy-induced plasticity may allow tumor cells to adopt alternative differentiation states that confer survival advantages under cytotoxic stress. In this context, squamous differentiation has been associated with relative resistance to radiation and chemotherapy in several tumor types.

A particularly notable feature of this case is the emergence of HPV16 in the SCC after treatment.

While HPV is a well-established etiological factor in SCC of the cervix, oropharynx, and anal canal, its role in colorectal carcinogenesis remains controversial [27, 28]. Reported HPV prevalence in colorectal AC varies widely, partly due to methodological differences in detection [29].

Viral infection may act as a co-factor facilitating epigenetic instability and altered differentiation programs.

The detection of HPV16 DNA in the post-treatment tumor raises the suggestion that viral infection may have contributed to the observed phenotype. However, since HPV status was not assessed in the primary tumor, the role of HPV in this process remains hypothetical.

Clinically, this case underscores the importance of thorough pathological reassessment following

neoadjuvant therapy, as tumor biology and phenotype may change substantially during treatment. HPV testing by PCR may be considered in p16-positive colorectal carcinomas or in tumors demonstrating unexpected phenotypic shifts, particularly when therapeutic resistance is observed [30, 31].

An important feature of this case is the clear temporal and morphological sequence documented by multiple baseline biopsies and subsequent examination of the entire resection specimen. The primary tumor demonstrated a conventional intestinal AC phenotype, whereas the post-treatment tumor consisted exclusively of poorly differentiated SCC without residual glandular structures. This striking shift in dominant lineage strongly supports the concept of therapy-associated phenotypic plasticity rather than simple sampling variation.

This study has several limitations. HPV testing of the primary tumor was not performed due to the lack of residual biopsy material, precluding retrospective molecular analysis. In addition, no clonal or genomic profiling was conducted. These limitations restrict the ability to fully elucidate the mechanisms underlying the observed phenotypic transformation. Therefore, these results should be interpreted with caution, as the available clinicopathological data do not allow a definitive distinction between true transdifferentiation and therapy-related clonal selection of a pre-existing squamous subclone.

To sum up, this case illustrates a rare phenotypic shift from rectal AC to HPV16-positive SCC following total neoadjuvant chemoradiotherapy. The findings support the concept of therapy-associated tumor plasticity and suggest a potential, yet unproven, role of HPV in lineage reprogramming under treatment-induced selective pressure. Careful pathological reassessment after neoadjuvant therapy is essential in rectal cancer, particularly in tumors with atypical differentiation. Further molecular and genomic studies are required to clarify the biological mechanisms and clinical implications of therapy-associated phenotypic shifts in colorectal malignancies.

Conflict of interest statement

The authors declare no competing interests.

Consent

Written informed consent for publication of this clinical case and accompanying images was obtained from the patient. A copy of the signed consent form is available to the journal's Editor-in-Chief upon request.

REFERENCES

1. Astaras C, Bornand A, Koessler T. Squamous rectal carcinoma: A rare malignancy, literature review and management recommendations. *ESMO Open*. 2021;6(4):100180. https://doi.org/10.1016/j.esmoop.2021.100180
2. Parente P, Mastracci L, Vanoli A, et al. Colorectal adenosquamous carcinoma: Peculiar morphology and different immunoprofiles in squamous and glandular components. *Pathol Res Pract*. 2022;238:153967. https://doi.org/10.1016/j.prp.2022.153967
3. Hanahan D. Hallmarks of cancer: New dimensions. *Cancer Discov*. 2022;12(1):31-46. https://doi.org/10.1158/2159-8290.CD-21-1059
4. Kovalyov OO, Tolok OP, Kovalyov KO. Transformation of adenocarcinoma into small cell lung cancer as a mechanism of acquired resistance to EGFR tyrosine kinase inhibitors. *Pathologia*. 2024;21(1):84-88. https://doi.org/10.14739/2310-1237.2024.1.298373
5. Shi ZJ, Pan K, Wu ZX, et al. Plasticity of tumor cells in targeted therapy-induced resistance: Mechanisms and new strategies. *Signal Transduct Target Ther*. 2023;8(1):113. https://doi.org/10.1038/s41392-023-01383-x
6. Fioretsaki R, Trifylli EM, Sarantis P, et al. The interplay between esophageal adenocarcinoma and its tumor microenvironment: Toward innovative therapies. *Cells*. 2025;14(23):1895. https://doi.org/10.3390/cells14231895
7. Wang X, Tan C, Wu K, et al. Integrative investigation of adeno-to-squamous transition in lung cancer resistance to EGFR-TKI identifies RAPGEF3 as a therapeutic target. *Natl Sci Rev*. 2024;11(12):nwae392. https://doi.org/10.1093/nsr/nwae392
8. Zhong J, Yang L. Histological transformation of rectal adenocarcinoma into choriocarcinoma after surgery and chemotherapy: A rare clinical case and literature review. *Int J Surg Case Rep*. 2024;117:109478. https://doi.org/10.1016/j.ijscr.2024.109478
9. Johnson GRJ, Park J, Helewa RM, et al. Total neoadjuvant therapy for rectal cancer: A guide for surgeons. *Can J Surg*. 2023;66(2):E196-E201. https://doi.org/10.1503/cjs.005822

10. Yasui K, Kondo R, Iizuka A, et al. Influence of preoperative chemoradiotherapy on the immunological status of patients with rectal cancer. *J Radiat Res*. 2020;61(5):766-775. https://doi.org/10.1093/jrr/rraa041
11. Zhou L, Zhu J, Liu Y, et al. Mechanisms of radiation-induced tissue damage. *MedComm (2020)*. 2024;5(10):e725. https://doi.org/10.1002/mco2.725
12. Makadia S, Patel I, Abusaada K. Human papillomavirus-positive squamous cell carcinoma of the rectum. *Cureus*. 2020;12(7):e9022. https://doi.org/10.7759/cureus.9022
13. Adetiloye AO, Asif A, Badero OJ, et al. Rare diagnosis of HPV-positive rectal squamous cell carcinoma in a 59-year-old heterosexual woman: Implications for screening recommendations. *Am J Case Rep*. 2025;26:e950554. https://doi.org/10.12659/AJCR.950554
14. Javadi M, Jalilian S, Kanani M, et al. Time to take HPV infection more seriously in colorectal cancer patients. *Front Med (Lausanne)*. 2024;11:1418359. https://doi.org/10.3389/fmed.2024.1418359
15. Lieb DA, Thompson HM, Verheij FS, et al. Colonic adenosquamous carcinoma: A single-center review of patient clinicopathologic characteristics, genetics, and clinical outcomes. *Cancers (Basel)*. 2024;16(15):2641. https://doi.org/10.3390/cancers16152641
16. Basavaraj S, Saniha PB, Geethalakshmi U, et al. Primary adenosquamous carcinoma of ascending colon: A rare entity. *J Med Sci Health*. 2022;8(3):288-291. https://doi.org/10.46347/jmsh.v8i3.22.350
17. Chohan S, Ahuja S, Sharma A, et al. Collision-type adenosquamous carcinoma of the colon with signet-ring adenocarcinoma: A rare case report. *Int J Surg Case Rep*. 2025;127:110808. https://doi.org/10.1016/j.ijscr.2024.110808
18. Nagtegaal ID, Odze RD, Klimstra D, et al. The WHO classification of tumours of the digestive system. *Histopathology*. 2020;76(2):182-188. https://doi.org/10.1111/his.13975
19. Nishi T, Weinstein WM, Makuuchi H. Squamous cell metaplasia in the rectum: A case report and review of the medical literature. *Tokai J Exp Clin Med*. 2004;29(4):163-166. PMID: 15717487
20. Parks A, Jovanov A. HPV, anal and rectal cancer: Gender norms and screening disparities. In: Vannelli A, editor. *Rectal and Anal Diseases*. London: IntechOpen; 2025. https://doi.org/10.5772/intechopen.1008798
21. Pan PH, Luo CW, Ting WC, et al. Impact of ascending HPV infection on the risk of colorectal cancer. *Microorganisms*. 2024;12:1746. https://doi.org/10.3390/microorganisms12091746
22. Mitoyan L, Chevrier V, Hernandez-Vargas H, et al. A stem cell population at the anorectal junction maintains homeostasis and participates in tissue regeneration. *Nat Commun*. 2021;12:2761. https://doi.org/10.1038/s41467-021-23034-x
23. Gupta PB, Pastushenko I, Skibinski A, et al. Phenotypic plasticity: Driver of cancer initiation, progression, and therapy resistance. *Cell Stem Cell*. 2019;24(1):65-78. https://doi.org/10.1016/j.stem.2018.11.011
24. Liu YP, Zheng CC, Huang YN, et al. Molecular mechanisms of chemo- and radiotherapy resistance and the potential implications for cancer treatment. *MedComm (2020)*. 2021;2(3):315-340. https://doi.org/10.1002/mco2.55
25. Micu A, Diaconescu A, Mincuna CE, et al. Overcoming the challenge: Resistance to neoadjuvant treatment in rectal cancer. *J Gastrointest Cancer*. 2025;56:205. https://doi.org/10.1007/s12029-025-01324-7
26. Zhang N, Tong H, Ji H. Squamous transition drives drug resistance. *Clin Transl Med*. 2024;14(6):e1697. https://doi.org/10.1002/ctm2.1697
27. Audeau A, Han HW, Johnston MJ, et al. Does human papillomavirus have a role in squamous cell carcinoma of the colon and upper rectum? *Eur J Surg Oncol*. 2002;28(6):657-660. https://doi.org/10.1053/ejso.2002.1304
28. Hsu CH, Lin YJ, Chen YC, et al. Human papillomavirus and risk of colorectal cancer: An analysis of nationwide claims data. *Medicina (Kaunas)*. 2022;58(10):1461. https://doi.org/10.3390/medicina58101461
29. Santos NC, Tocantins P, Leão-Cordeiro JAB, et al. The human papillomavirus in colorectal cancer. *J Med Sci*. 2021;42(1):1-7. https://doi.org/10.4103/jmedsci.jmedsci_194_20
30. Dalla Libera LS, de Siqueira T, Santos IL, et al. Detection of human papillomavirus and the role of p16INK4a in colorectal carcinomas. *PLoS One*. 2020;15(6):e0235065. https://doi.org/10.1371/journal.pone.0235065
31. Hafez F, Refaat G, Alorabi M, et al. Interpretation of p16 expression as a marker of HPV in colorectal carcinoma. *Histol Histopathol*. 2022;37(5):455-463. https://doi.org/10.14670/HH-18-439

Submitted: February 02, 2026

О. Ковальов [1], С. Завгородній [1], О. Толок [2], А. Аненко [2],
М. Кубрак [1], М. Данилюк [1], К. Ковальов [1]

[1] Запорізький державний медико-фармацевтичний університет, Запоріжжя, Україна
[2] Медичний онкологічний центр ЮЛІС, Запоріжжя, Україна

ФЕНОТИПОВИЙ ЗСУВ АДЕНОКАРЦИНОМИ В ПЛОСКОКЛІТИННИЙ РАК ПРЯМОЇ КИШКИ ПІСЛЯ НЕОАД'ЮВАНТНОЇ ХІМІОПРОМЕНЕВОЇ ТЕРАПІЇ З ВИЯВЛЕННЯМ ВПЛ16: КЛІНІЧНИЙ ВИПАДОК

Аденосквамозний рак та істинно плоскоклітинний рак прямої кишки є надзвичайно рідкісними злоякісними новоутвореннями, що становлять приблизно 0,15% усіх випадків колоректального раку. У поодиноких випадках неоад'ювантна хіміопроменева терапія може супроводжуватися істотними змінами в диференціюванні пухлинних клітин, однак біологічні механізми таких змін з'ясовані недостатньо. У повідомленні наведено випадок місцево поширеної аденокарциноми прямої кишки (cT4bN2M0) у жінки, яка отримала тотальну неоад'ювантну терапію, що включала хіміотерапію за схемою XELOX у поєднанні з променевою терапією малого таза. Первинні біопсійні зразки, отримані з кількох ділянок пухлини, підтвердили наявність помірно диференційованої аденокарциноми з типовим кишковим імунофенотипом. Після лікування в резектованій пухлині відзначено повну втрату маркерів CK20, CDX2 та появу плоскоклітинного імунофенотипу з позитивною експресією p40 і p63. Гістологічно пухлина була представлена виключно низькодиференційованою плоскоклітинною карциномою. За результатами ПЛР-аналізу в плоскоклітинному компоненті пухлини виявлено ДНК вірусу папіломи людини 16-го типу (ВПЛ16). Виражена дифузна експресія $p16^{INK4a}$ спостерігалась як у первинній аденокарциномі, так і в пухлині після лікування. Отримані результати свідчать про виражений асоційований з терапією фенотиповий зсув у диференціації пухлини. Водночас точний біологічний механізм цього явища залишається невизначеним. Серед можливих пояснень розглядаються індукована терапією пухлинна пластичність, клональна селекція раніше існуючого плоскоклітинного субклону або первинно нерозпізнаний змішаний пухлинний фенотип. Представлений випадок підкреслює важливість ретельної патоморфологічної повторної оцінки пухлин після неоад'ювантної терапії при раку прямої кишки та демонструє складність інтерпретації фенотипових змін у пухлинах після лікування. Потенційна роль ВПЛ в таких процесах залишається гіпотетичною і потребує подальших досліджень.

Ключові слова: аденокарцинома прямої кишки, плоскоклітинна трансдиференціація, ВПЛ16, неоад'ювантна хіміопроменева терапія.