Case report

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# Immunochemotherapy in metastatic cervical cancer: an innovative approach for better treatment outcome

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Immune checkpoint inhibitors (ICIs) enhance antitumor immunity by blocking regulatory pathways that normally limit immune activation, thereby restoring the immune system's ability to recognize and eliminate cancer cells.

We present the case of a patient diagnosed with cervical cancer, who first experienced symptoms two years ago. A cervical biopsy was performed, and histopathological analysis confirmed a diagnosis of squamous cell carcinoma of the cervix. Following a thorough gynecological examination and diagnostic work-up, the disease was staged as FIGO IIb cervical cancer. Treatment was administered according to the standard cervical cancer protocol, consisting of chemoradiotherapy, as imaging and laboratory findings showed no involvement of other parenchymal organs. One year after completing treatment, a thoracic MSCT revealed disease progression in the lungs, with multiple pulmonary metastases. According to current protocols for the treatment of metastatic cervical cancer, the patient was started on immunochemotherapy with pembrolizumab in combination with paclitaxel and carboplatin. The patient

received immunochemotherapy, with pembrolizumab administered at a fixed dose of 200 mg intravenously every three weeks, PD-L1 expression status was 10. Paclitaxel was administered at 175 mg/m² and carboplatin at an AUC of 5. Treatment response was monitored using thoracic MSCT, abdominal and pelvic MRI and evaluated according to iRECIST criteria. After the fourth cycle of immunochemotherapy, thoracic MSCT confirmed a significant therapeutic response, demonstrating partial remission of pulmonary metastases.

Immunotherapy, especially ICIs, has markedly advanced the treatment landscape for cervical cancer, improving overall and progression-free survival and response rates in recurrent or metastatic disease.

Key words: Immunotherapy, chemotherapy, cervical cancer

Prikaz slučaja

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# Imunohemioterapija kod metastatskog karcinoma grlića materice: inovativni pristup za bolji terapijski ishod

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Inhibitori imunoloških kontrolnih tačaka pojačavaju antitumorski imunski odgovor blokiranjem regulatornih puteva koji u fiziološkim uslovima ograničavaju aktivaciju imunskog sistema, čime se ponovo uspostavlja sposobnost imunskog sistema da prepozna i eliminiše maligne ćelije.

Prikazujemo slučaj pacijentkinje sa dijagnozom karcinoma grlića materice, kod koje su se prvi simptomi javili pre dve godine. Urađena je biopsija grlića materice, a histopatološkom analizom potvrđen planocelularni karcinom grlića materice. Nakon kompletne dijagnostičke obrade, utvrđeno je da se radi o karcinomu grlića materice FIGO IIb. Lečenje je sprovedeno u skladu sa standardnim protokolima za lečenje karcinoma grlića materice koji podrazumeva sprovođenje hemioradioterapije. Godinu dana nakon završetka lečenja, MSCT grudnog koša pokazao je progresiju bolesti u plućima, sa prisustvom multiplih metastaza. U skladu sa važećim protokolima za lečenje metastatskog karcinoma grlića materice, započeta je imunoterapija u kombinaciji sa hemioterapijom, uz primenu pembrolizumaba sa

paklitakselom i karboplatinom. Pacijentkinja je primala imunohemioterapiju, pri čemu je pembrolizumab dat u fiksnoj dozi od 200 mg intravenski na svake tri nedelje. Paklitaksel je primenjivan u dozi od 175 mg/m², a karboplatin u dozi AUC 5. Terapijski odgovor je praćen na MSCT grudnog koša, MR abdomena I male karlice i procenjivan prema iRECIST kriterijumima. Nakon četvrtog ciklusa imunohimioterapije, MSCT grudnog koša je potvrdio značajan terapijski odgovor, uz postizanje parcijalne remisije metastaza na plućima.

Imunoterapija, posebno primena inhibitora imunoloških kontrolnih tačaka, značajno je unapredila terapijske mogućnosti u lečenju karcinoma grlića materice, dovodeći do poboljšanja ukupnog i preživljavanja bez progresije bolesti, kao i većih stopa terapijskog odgovora kod bolesnica sa recidivantnom ili metastatskom bolešću

Ključne reči: imunoterapija, hemioterapija, karcinom grlića materice

## Introduction

Cervical cancer is predominantly caused by persistent infection with high-risk human papillomavirus (HPV) types, particularly HPV16 and HPV18, which promote malignant transformation through the activity of the E6 and E7 oncoproteins (1-3). These proteins disrupt critical tumor suppressor pathways by promoting the degradation of p53 and inactivating the retinoblastoma protein, resulting in uncontrolled cell cycle progression, genomic instability, and resistance to apoptosis (4,5). Because HPV-derived antigens are highly immunogenic, cervical cancer is an attractive target for immunotherapy, including checkpoint inhibitors, therapeutic vaccines, and adoptive cell-based treatments (6,7).

Immune checkpoint inhibitors (ICIs) enhance antitumor immunity by blocking regulatory pathways that normally limit immune activation, thereby restoring the immune system's ability to recognize and eliminate cancer cells. Tumor cells frequently exploit these immune checkpoints to avoid immune surveillance (8). ICIs primarily target the PD-1/PD-L1 and CTLA-4 pathways, with CTLA-4 functioning mainly during the early phase of T-cell activation in lymphoid organs, while the PD-1/PD-L1 axis predominantly regulates T-cell responses at later stages within peripheral tissues (9). By inhibiting immune checkpoint pathways, ICIs restore effective antitumor immune responses, representing a powerful strategy in cancer treatment; however, this generalized enhancement of T-cell activity may also result in immune-related adverse events due to loss of immune tolerance toward healthy tissues (10).

## Case report

We present the case of a patient diagnosed with cervical cancer, who first experienced symptoms two years ago, including postmenopausal vaginal bleeding and lower abdominal pain. A cervical biopsy was performed, and histopathological analysis confirmed a diagnosis of squamous cell carcinoma of the cervix (Figure 1). Following a thorough gynecological examination and diagnostic work-up, the disease was staged as FIGO IIb cervical cancer. Treatment was administered according to the standard cervical cancer protocol, consisting of chemoradiotherapy, as imaging and laboratory findings showed no involvement of other parenchymal organs.

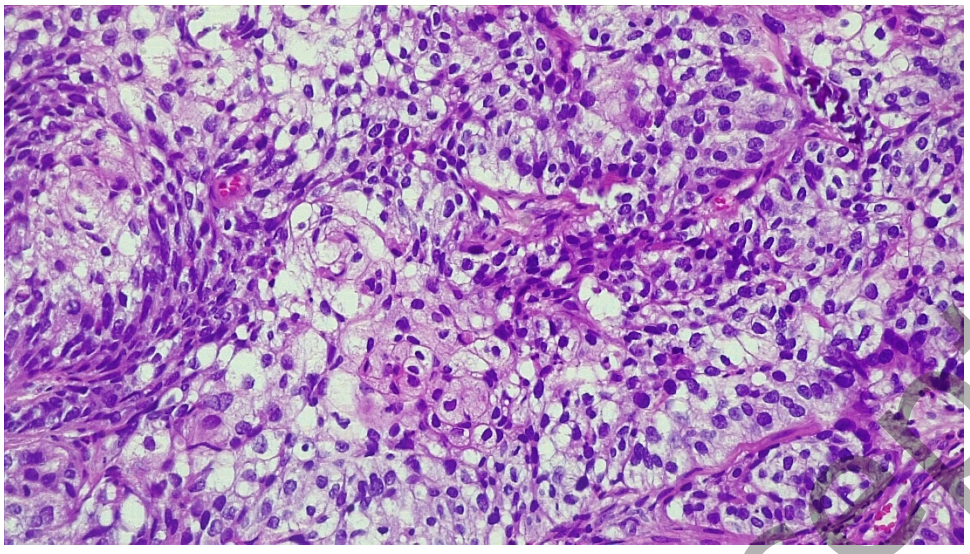

Figure 1. Micromorphology of non-keratinizing squamous cell carcinoma of the cervix. Neoplastic tissue consists of confluent solid tumor nests of atypical polygonal cells with hyperchromatic pleomorphic nuclei and pale cytoplasm (HE stain, original magnification x20).

One year after completing treatment, a thoracic MSCT revealed disease progression in the lungs, with multiple pulmonary metastases. The MSCT demonstrated several nodular lesions with stellate contours diffusely distributed in both lungs: seven in the right lung and one in the left lung. The largest nodule, located in segment S6, measured 11 mm. A morphologically distinct hilar lesion was observed in the lower pole of the right hilum, measuring 20 mm, broad-based along the intermediate lobar bronchus and causing occlusion of the S7 segmental bronchus. No individually enlarged mediastinal lymph nodes or pleural effusion were noted (Figure 2.)

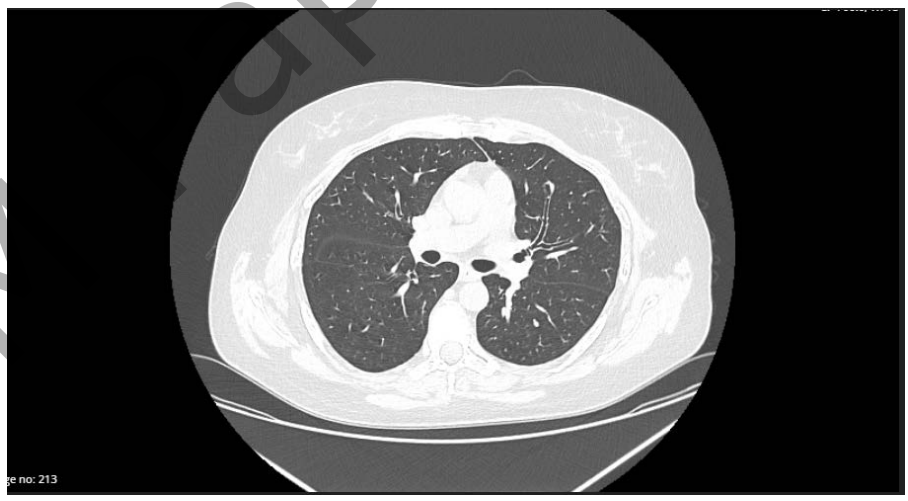

Figure 2. Thoracic MSCT before immunochemotherapy: T2W sequence

The pelvic MRI findings indicated stable disease. The uterus showed no changes compared to the previous examination, with an intramural anterior wall fibroid measuring up to 40 mm in diameter. The previously treated eccentric lesion on the right lateral aspect of the cervix remained morphologically and in signal characteristics unchanged, with no evidence of restricted diffusion, consistent with post-therapeutic fibrosis. There was residual thickening with increased signal intensity in the distal third of the vagina, indicative of evolving post-radiation changes. The ovaries were involuted and not visualized (Figure 3).

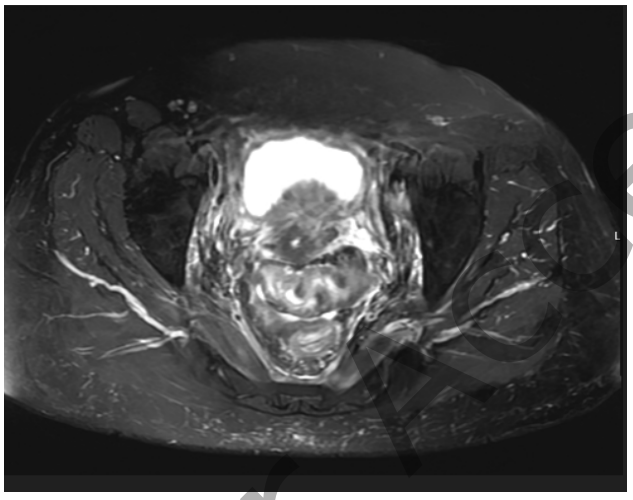

Figure 3. MRI of the pelvis

Abdominal MRI revealed no neoplastic infiltrative lesions in the parenchymal organs, neither ascites, nor retroperitoneal lymphadenopathy.

According to current protocols and European guidelines for the treatment of metastatic cervical cancer, the patient was started on immunochemotherapy with pembrolizumab in combination with paclitaxel and carboplatin.

Programmed cell death ligand 1 (PD-L1) status was assessed in tumor samples, revealing a combined positive score (CPS) greater than 1 (Figure 4). The patient received immunochemotherapy, with pembrolizumab administered at a fixed dose of 200 mg intravenously every three weeks, PD-L1 expression status was 10. Paclitaxel was administered at 175 mg/m² and carboplatin at an AUC of 5. Treatment response was monitored using thoracic MSCT, abdominal and pelvic MRI and evaluated according to iRECIST criteria.

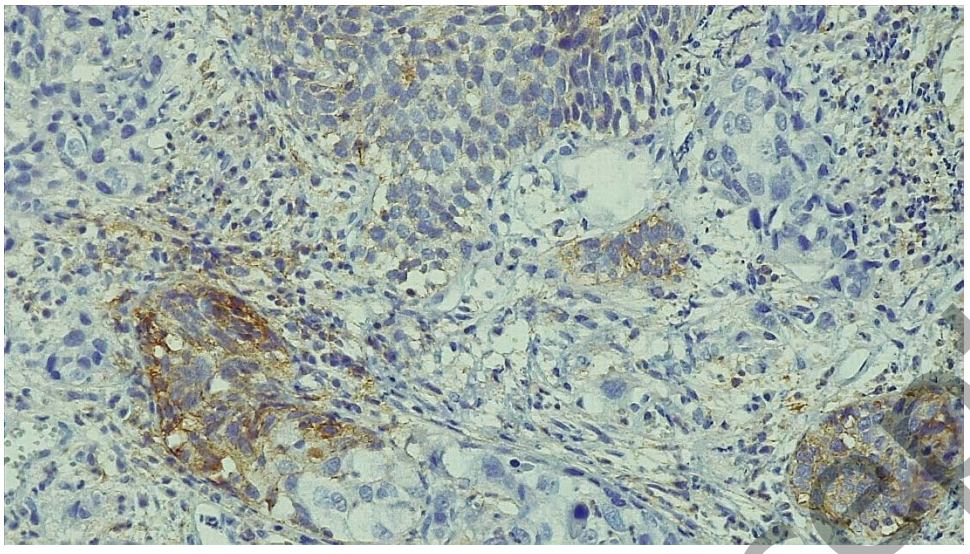

Figure 4. PD-L1 immunohistochemical expression in squamous cell cervical carcinoma. Positive membranous staining is visible on the membranes of tumor cells. In addition, some tumor infiltrating immune cells show cytoplasmic and membranous expression. In this case combined positive score was greater than 1 (CPS≥1) (PD-L1 clone 22C3, original magnification x20).

After the fourth cycle of immunochemotherapy, thoracic MSCT confirmed a significant therapeutic response, demonstrating partial remission of pulmonary metastases. Of the eight previously identified secondary lesions, only two remained, both substantially reduced in size: the S6 lesion in the right lung decreased from 11 mm to 6 mm, and the largest lesion in the right hilum was reduced to 9 mm. All residual lesions now exhibited features of fibrotic scarring without significant contrast enhancement. New lesions were not observed, and the mediastinum showed no individually enlarged lymph nodes or pleural effusion (Figure 5).

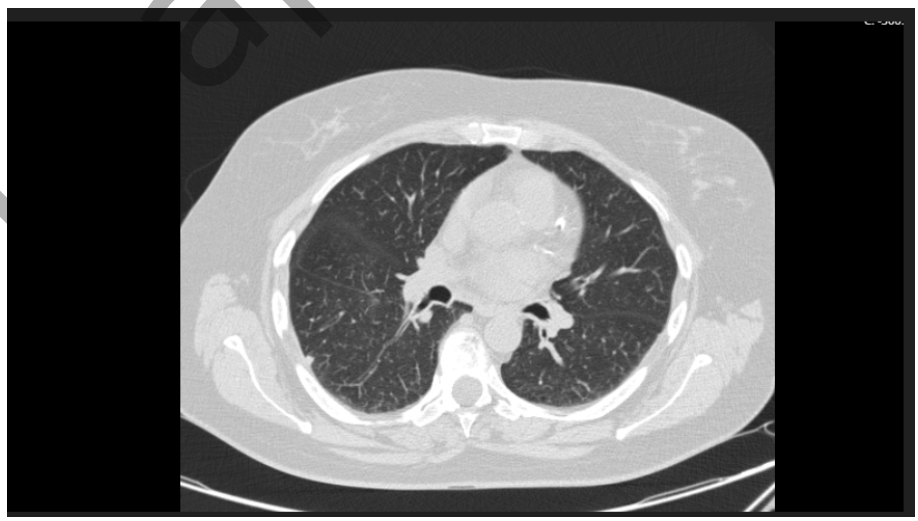

Figure 5. Thoracic MSCT after immunochemotherapy: T2W sequence

Abdominal and pelvic MRI findings confirmed stable disease. The patient's treatment was continued with immunochemotherapy.

## Discusion

Cervical cancer caused by a sexually transmitted infection, is largely preventable, and its global burden can be substantially reduced through comprehensive education about sexual health, screening programs such as Pap smears, HPV testing, and early medical intervention (11,12). Since the introduction of prophylactic vaccination cervical cancer prevention has markedly improved, particularly in populations with high mortality rates and in low-resource settings where access to routine screening is limited (13,14). By combining vaccination with continued education and early detection strategies, the overall burden of cervical cancer can be substantially reduced, preventing thousands of deaths each year and improving women's health outcomes globally (15,16).

In recurrent or metastatic cervical cancer, patients ineligible for surgery or radiotherapy are usually treated with systemic therapy. Multidrug regimens, particularly cisplatin plus paclitaxel, improve progression-free survival, though not median overall survival, and other cisplatin-based combinations such as cisplatin with topotecan, gemcitabine, or vinorelbine show no added benefit. The addition of biological agents, such as the VEGF inhibitor bevacizumab, to standard chemotherapy has improved overall survival, while PD-1 inhibitors such as pembrolizumab, either alone or with chemotherapy, improve outcomes (17). The KEYNOTE-028 trial showed that pembrolizumab was safe and effective in PD-L1–positive locally advanced and metastatic cervical cancer, with a median overall survival of 11 months and grade ≥3 adverse events in 20.8% of patients (18). KEYNOTE-158 further demonstrated durable antitumor activity, with all responders being PD-L1-positive (19). The KEYNOTE-826 study confirmed that pembrolizumab combined with chemotherapy, with or without bevacizumab, significantly improved overall survival compared to platinum-based chemotherapy in persistent, recurrent, or metastatic disease. Benefits were most pronounced in patients with a PD-L1 combined positive score (CPS) ≥1, highlighting PD-L1 as a potential predictive biomarker.The KEYNOTE-826 trial confirmed that pembrolizumab combined with multidrug chemotherapy significantly increases both overall and progression-free survival (20). In the ENGOT-cx11/GOG-3047/KEYNOTE-A18 trial (NCT04221945) involving 1,060 patients, pembrolizumab combined with concurrent chemoradiotherapy (CCRT, n=529) significantly improved progression-free survival compared with placebo plus CCRT (n=531), achieving a 24-month PFS of 67.8% versus 57.3% (P = 0.0020) (21). Differences between the CALLA (22) and KEYNOTE-A18 trials may be attributed to variations in patient populations, with KEYNOTE-A18 enrolling higher-risk patients based on lymph node size or number, as well as differences in sample size and the ICIs used. Two ongoing clinical trials are evaluating new approaches for advanced or metastatic cervical cancer. The PRIMMO trial (23) is testing pembrolizumab combined with chemoradiotherapy to enhance

antitumor immunity by modulating the tumor microenvironment. Meanwhile, the Phase I DURVIT trial (24) is investigating intratumoral durvalumab injections to control early metastatic spread via lymphatic drainage and potentially delay or prevent disease recurrence. In less heavily treated advanced cervical cancer, nivolumab showed a 26% overall response rate, including responses in PD-L1–negative tumors, indicating PD-L1 may not consistently predict outcomes. Similar observations have been made in melanoma. Fifteen trials have evaluated immune checkpoint inhibitors in cervical cancer, including pembrolizumab, nivolumab, and ipilimumab. Nivolumab monotherapy or combination therapy with ipilimumab showed promise in the CheckMate 358 study for recurrent or metastatic disease. Additionally, cadonilimab, a bispecific PD-1/CTLA-4 antibody, achieved a 33% overall response rate in the Phase Ib/II AK104-201-AU trial, with higher responses in PD-L1–positive patients (43.8%) and in squamous cell carcinoma (34%), while patients with adenocarcinoma did not respond (25).

## Conclusion

Immunotherapy, especially ICIs, has markedly advanced the treatment landscape for cervical cancer, improving overall and progression-free survival and response rates in recurrent or metastatic disease, including PD-L1–negative cases, and is now a first-line option. While promising in locally advanced disease and combination therapies, challenges remain in identifying reliable biomarkers and overcoming tumor resistance, with emerging strategies such as antibody-drug conjugates (ADCs) and CAR-T cell therapies showing potential.

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