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A rare and complete response to combination therapy with radiation and nivolumab in a patient with metastatic urothelial cancer

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SUMMARY

According to the current understanding, radiotherapy can enhance the effectiveness of cancer immunotherapy due to radiation-induced release of tumour-associated antigens. Here, we present a case with a metastatic urothelial carcinoma who received nivolumab and palliative radiotherapy to a residual tumour in the vagina and to a large metastatic visceral lymph node. The treatment resulted in a rapid and virtually complete response for the time being in all metastases and in the large paraaortic tumour mass. Follow up continues. The presented case demonstrates that the combinatory treatment with radiotherapy and immunotherapy can result in an exceptional response for the benefit of the patient with urothelial cancer. To our knowledge, this is one of the largest metastatic masses to disappear with a combination of immuno-oncologic (nivolumab) and radiation therapies.

BACKGROUND

Bladder cancer (BC) is the 10th most commonly diagnosed cancer worldwide with more than 570 000 new cases and over 158 000 deaths recorded in 2020.¹ Platinum-based chemotherapy is the first-line regimen for advanced or metastatic urothelial carcinoma (UC),² with an overall response rate of 49% with gemcitabine/cisplatin (GC).³ However, roughly half of the patients diagnosed with BC are not eligible for platinum-based chemotherapy, due to numerous comorbidities including renal and cardiac dysfunction.^{4,5} Until the introduction of immune checkpoint inhibitors for the treatment of BC, the therapy options for platinum-ineligible patients or patients with post-platinum progression were scarce.⁶ Currently, four immune checkpoint inhibitors have been approved by the US Food and Drug Administration (FDA), for the treatment of locally advanced or metastatic urothelial cancer.^{7,8}

The molecular basis of immune checkpoints lies in transmembrane checkpoint proteins, such as the programmed cell death 1 (PD-1) and the programmed death ligand-1 (PD-L1). Binding of PD-L1 on tumour cells to the PD-1 receptor on T cells results in T-cell exhaustion and abnormal inactivation of T-cell-mediated antitumour immunity.⁹ Checkpoint targeting cancer immunotherapies rely on monoclonal antibodies that block the interaction between PD-1 and PD-L1 and thereby reinvigorate the antitumour immunity.^{9,10} Nivolumab (OPDIVO) is a human IgG4 antibody, which by binding to PD-1 restores the antitumour activity

of T cells. Nivolumab was approved for second-line treatment after platinum-based chemotherapy in metastatic UC by FDA and European Medicine Agency (EMA) after the CheckMate 275 multi-centre, single-arm, phase 2 trial.¹¹ The median overall survival was reported to be 5.95 months in a subgroup, where <1% of tumour cells expressed PD-L1 and 11.3 months in a subgroup where the expression was ≥1% (investigated with Dako PD-L1 immunohistochemical 28-8 pharmDx kit). The median overall survival in the overall treated population was 8.74 months, which surpasses the 6.98 months of pooled median overall survival observed with single-drug chemotherapies.¹²

Radiation therapy leads to tumour cell death and subsequent release of cytokines and other tumour-associated neoantigens. Antigen-presenting cells, such as dendritic cells (DCs), process the neoantigens into peptides and display them on their cell surfaces in complex with the major histocompatibility class II molecules. DC-mediated presentation of the antigens to cytotoxic T cells results in T-cell priming and subsequent activation of T-cell dependent tumour elimination mechanisms.¹³ The current understanding is that cancer immunotherapy can further enhance this effect by inhibiting the PD-L1-mediated inactivation of T cells.^{9,14}

Deep and long-lasting responses to immunotherapy scheduled soon after or simultaneously with radiotherapy have been reported in patients with advanced UC. Magalhães and colleagues reported in 2021 a case of unresectable oligometastatic UC that was treated with radiotherapy with a total dose of 56 Gy to pelvic lesion leading to lesion stabilisation at size 50×31 mm.¹⁵ Due to renal impairment, the patient was considered ineligible for chemotherapy and thus atezolizumab was initiated as the first-line therapy in April 2018. After four cycles of treatment, CT scan showed a complete response. The treatment was later terminated due to impaired renal function, yet the complete response maintained for several years. Excellent response to combination therapy was also observed in a patient with UC with metastases in the breast, thoracic wall and para-aortic lymph nodes.¹⁶ The patient received pembrolizumab as a second-line therapy after GC, together with stereotactic radiotherapy with a total dose of 30 Gy in three fractions to the breast and thoracic wall metastases. Intriguingly, the combination of radiotherapy and four cycles of pembrolizumab led to complete response in all disease sites.¹⁶



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Here, we present a case of a woman with a widespread metastatic UC, who after failed GC treatment received nivolumab and palliative radiotherapy to a residual tumour in the vagina and to a large metastatic visceral lymph node. CT imaging revealed a complete response to the treatment and radiographic finding was in line with excellent symptom relief. The opioids were no longer needed, and the patient was able get back to work and return to her old lifestyle with hiking and other outdoor activities.

CASE PRESENTATION

In the spring 4 years ago, a non-smoking woman in her 50s came to the emergency room suffering from macroscopic haematuria and flank pain. The patient was examined with CT imaging, which identified a putative tumour in the bladder and bilateral hydronephrosis. Transurethral resection of bladder tumour (TURBT) was performed, and the left ureter was stented. Nephrostomy was placed on the right kidney, as the ureteric orifice could not be identified. Pathological assessment of the tumour demonstrated a high-grade muscle invasive UC. The patient received reduced neoadjuvant doses of GC due to declined glomerular filtration rate. Gemcitabine 1000 mg/m² (dose reduction 30%) on days 1, 8, 15 and cisplatin 70 mg/m² (dose reduction 30%) on day 2 was administered every 4 weeks for three full cycles. A robotic-assisted laparoscopic cystectomy, with extended pelvic lymphadenectomy, resection of the uterus, ovaries and the top of vagina, was performed together with Bricker ileal conduit diversion.

In the beginning of the following year, we observed new metastases in the lungs and a large residual tumour contacting the vagina. The administration of GC was reinitiated with gemcitabine 1000 mg/m² (dose reduction 30%–40%) on days 1, 8, 15 and cisplatin 70 mg/m² (dose reduction 30%–35%) on day 2 every 4 weeks for three cycles. The third cycle was stopped on day 2 due to symptomatic disease progression. The tumour continued to grow through the vaginal wall and resulted in vaginal bleeding. Consequently, the patient received palliative radiotherapy of 30 Gy to the vaginal tumour and the bleeding stopped. Six months later, nivolumab was initiated with a fixed dose of 240 mg once every 2 weeks and it was later on administered with approved dosing schedules 240 mg once every 2 weeks or 480 mg once every 4 weeks. A CT scan was performed 6 months after the treatment initiation, which revealed that the metastases in the lungs as well as the residual tumour contacting the vagina had responded well to the treatment. However, an additional metastasis in the lymph node next to the right iliac veins had substantially grown (7.7×6.2 cm) irrespective of the immuno-oncologic (IO) treatment. This resulted in increased pain in the groin area and in the lower limb. In the beginning of next year, the patient received palliative radiotherapy of 12 Gy to the parailiac metastasis simultaneously to the ongoing nivolumab treatment. For the schematic presentation of the treatment scheme and patient medical history, please see figure 1A.

OUTCOME AND FOLLOW-UP

Three months after the second palliative radiotherapy, we observed a complete response to the treatment in the CT scan (figure 1B, right). Practically the entire tumour mass had disappeared, and the overall condition of the patient had markedly improved. In the following CT scan performed 3 months later, the complete response was maintained for time being and the requirement for pain medication had ended. Furthermore, the physical condition of the patient had considerably improved

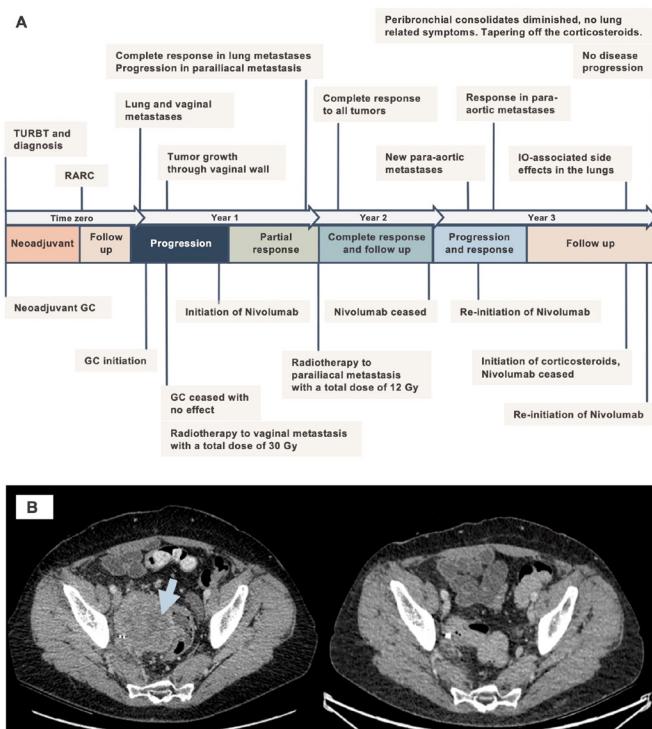


Figure 1 (A) Time line of the medical history of the patient. The time line was created by a coauthor (JJ), (B) CT scan images of the patient (transverse plane at level low in the pelvis). On the left, the state of the patient at 1 year and 6 months after the initial diagnosis, large parailiac metastatic mass indicated with blue arrow. On the right, the state at 1 year and 9 months after the initial diagnosis, after 12 Gy palliative radiotherapy, the tumour mass had disappeared. The authors have the permission to use the images. The image layout was created by a coauthor (AH). GC, gemcitabine/cisplatin chemotherapy; RARC, robotic-assisted laparoscopic radical cystectomy; TURBT, transurethral resection of bladder tumour.

allowing her to return to predisease exercise scheme and back to her old job. After 9 months of complete response, the nivolumab treatment was discontinued. We propose that the exceptional response was achieved by combining PD-1-targeting antibody therapy and radiotherapy.

For further understanding of the clinical behaviour of the tumour and to contemplate on the mechanisms behind the observed excellent response, we performed retrospective immunohistochemical analyses on the primary tumour samples. The expression of PD-1 was assessed with monoclonal mouse anti-human PD-1 clone NAT105 (Abcam, Cambridge, UK) and PD-L1 with a monoclonal rabbit anti-human PD-L1 clone E1L3N (Cell Signaling Technology, Danvers, Massachusetts, USA). Interestingly, PD-1 and PD-L1 protein expression was detected in the primary tumour excised from the bladder (figure 2), indicating that the cancer-associated immune evasion mechanisms were activated in the primary tumour. Although focusing only on the primary tumour, these results are in line with previous findings, where strong expression of PD-L1 in bladder tumours has been shown to positively correlate with good response to combination of immune checkpoint inhibitors and radiotherapy.¹⁴

In the beginning of last year, a new para-aortic lymph node metastasis was observed and the administration of nivolumab was reinitiated considering the good and long-lasting response to previous treatment. Retreatment with nivolumab resulted in a partial response as the para-aortic lymph node metastasis

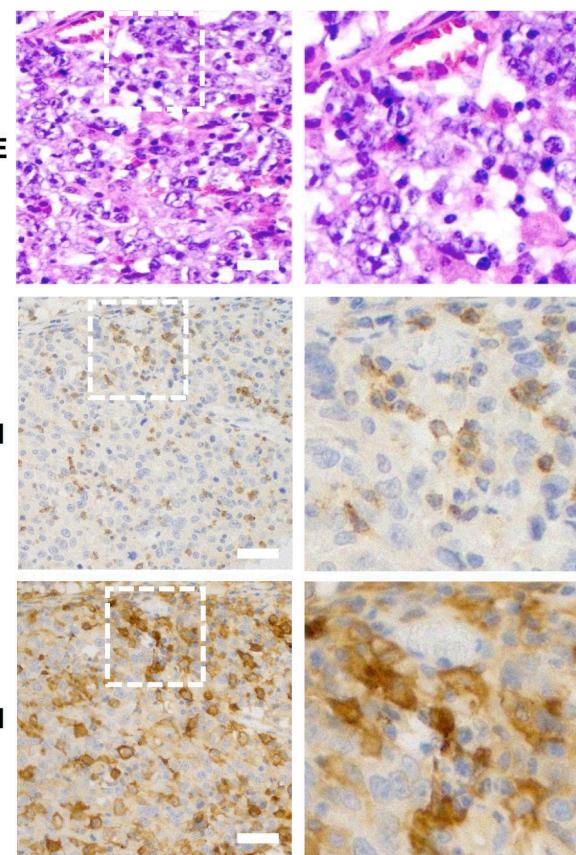


Figure 2 Histological analysis of the primary tumour in the bladder. Formalin-fixed paraffin-embedded tumour tissue was stained with HE. Immunohistochemical staining was performed with anti-PD-1 and anti-PD-L1 antibodies. The insets of the indicated areas are shown in right panel. Images were obtained with ManualWSI whole slide scanner (Microvisioneere, Esslingen am Neckar, Germany) with 40× magnification. Scale bar 50 µm. Imaging was performed and the image layout generated by a coauthor (JJ). PD-1, programmed cell death 1; PD-L1, programmed death-ligand-1.

was found diminished. In the following CT scan, mildly symptomatic peribronchial consolidates were detected in both lungs. The radiological finding suited primarily to Grade 2 (Common Terminology Criteria for Adverse Events, CTCAE, grading scale) IO pneumonitis. Due to the observations, nivolumab treatment was ceased, and the patient was treated with per oral prednisolone 1 mg/kg. By the end of last year, the peribronchial consolidates had markedly diminished and the patient reported no lung-related symptoms. The treatment with nivolumab was yet again reinitiated.

DISCUSSION

Variable cisplatin combinations are the golden standard for the first-line treatment of metastatic or inoperable UC.² However, the treatment strategy presents a considerable challenge, since approximately 40% of the patients are not applicable for the treatment due to poor performance status, decreased renal function and platinum-related serious adverse effects.¹⁷ Today, several immune checkpoint PD-1/PD-L1 inhibitors (atezolizumab, avelumab, nivolumab and pembrolizumab) have been shown to be effective in the treatment of locally advanced or metastatic UC. From the used antibodies, atezolizumab and pembrolizumab are an alternative first-line therapy option for

cisplatin unfit PD-L1 positive patients.¹⁸ Nivolumab is used in the second line after platinum-based treatment by EMA's acceptance in Europe.¹¹

Roughly 20% of the patients treated with immune checkpoint inhibitors will respond to treatment.¹⁹ There have been several studies indicating that irradiation can increase the effectiveness of immunotherapies in BC.²⁰ Currently, there are several ongoing phase II and III studies trying to increase the treatment response rates by combining chemotherapy or radiotherapy to immunotherapy-based treatments.²¹

Combined immunotherapy and radiotherapy are thought to enhance the cancer treatment responses by radiotherapy-induced release of circulating tumour neoantigens consequently leading to more effective activation of tumour-specific cytotoxic T cells that have the ability to elicit their effects also at distant tumour sites.¹⁷ Previous studies and case reports have demonstrated that combination of radiotherapy and immunotherapy can in some cases also result in a strong and universal abscopal-like treatment response outside the radiation target site.^{9 17} Here, we report a case, where a patient with aggressive metastatic UC achieved a complete response after immune-oncological treatment and palliative radiotherapy. We found that PD-L1, an inhibitory checkpoint protein, was highly expressed in the primary tumour.

Previous studies have hypothesised that immunotherapy might also enhance the effectiveness of chemotherapy. In IMvigor130 trial, they compared atezolizumab with chemotherapy versus chemotherapy versus atezolizumab alone.²² The KEYNOTE 361 compared pembrolizumab versus pembrolizumab plus chemotherapy versus chemotherapy.²³ In the third study (DANUBE), Powles and colleagues compared combination of cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor tremelimumab and durvalumab versus chemotherapy versus durvalumab.²⁴ The

Patient's perspective

Translated from Finnish to English according to patient's briefing by the authors.

"The time in chemotherapy was challenging. The infusion time was long and the reaction in my body lasted for several days with different kinds of adverse effects. During the immunotherapy, the infusion time was considerably shorter, and I experienced the treatment to be gentler than chemotherapy. I experienced only mild tiredness for few days after the treatment, which helped the return to normal everyday life. The most unpleasant symptoms were localised to oral mucosa. For me personally, the most important thing is of course that the treatment has helped me. However, I consider this case report to be also highly significant, because if it can help even one patient to get this treatment and have a good response, it has all been worth it."

Learning points

- Immunotherapy is a viable treatment option after failed cisplatin-based chemotherapy in patients with muscle invasive bladder cancer.
- Radiotherapy enhances the effectiveness of immune checkpoint inhibitors in metastatic bladder cancer.
- A subset of patients with urothelial cancer will likely benefit from retreatment with nivolumab after once ceased treatment.

results from these three large phase III studies unfortunately failed to show overall survival benefit of combining IO therapy to platinum-based chemotherapy over chemotherapy only.^{22–24} Thereby, modern immunotherapies are valuable addition to the repertoire of cancer treatments but at least thus far, they cannot fully replace chemotherapy in metastatic UC.

Currently, the optimal treatment sequence after complete or long-lasting partial response is not known. The initial studies investigating the immune checkpoint inhibitors for the treatment of metastatic UC were designed to continue the treatment until progression or serious adverse effects were detected, or up to 24 months.^{11–25} Several currently ongoing studies are aiming to identify the optimal time to cease the treatment.²⁶ In a retrospective study, retreatment of once ceased immunotherapy with nivolumab in non-small cell lung cancer appeared to be beneficial.²⁷ After a robust complete response to immunotherapy, the treatment is often paused and reinitiated if signs of disease progression are observed during follow-up. In the presented case, new long-lasting response was achieved with nivolumab retreatment, suggesting that reinitiation of the treatment might be beneficial also when treating patients with UC.

Our case is a presentation of metastatic UC with an exceptional response in large metastases to the combination of radiotherapy and immunotherapy. Our patient also benefited from the retreatment with nivolumab after cancer relapse. Together with the ongoing clinical trials, this case provides evidence that the combinatory treatment strategy is beneficial even for patients with metastatic and platinum pretreated UC.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

REFERENCES

- 1 Ferlay J, Laversanne M, Ervik M. Global cancer Observatory: cancer tomorrow. Lyon, France: international agency for research on cancer, 2020. Available: <https://gco.iarc.fr/tomorrow> [Accessed 30 May 2021].
- 2 Gajate P, Torres-Jiménez J, Bueno-Bravo C, et al. Practice change in the management of metastatic urothelial carcinoma after ASCO 2020. *World J Clin Oncol* 2020;11:976–82.
- 3 von der Maase H, Sengelov L, Roberts JT, et al. Long-Term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602–8.
- 4 Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer* 2006;107:506–13.
- 5 von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068–77.
- 6 Sweiis RF, Galsky MD. Emerging role of immunotherapy in urothelial carcinoma—Immunobiology/biomarkers. *Urol Oncol* 2016;34:556–65.
- 7 Rhea LP, Mendez-Marti S, Kim D, et al. Role of immunotherapy in bladder cancer. *Cancer Treat Res Commun* 2021;26:100296.
- 8 Voluntary withdrawal of Imfinzi indication in advanced bladder cancer in the US, 2021. Available: <https://bit.ly/2ZGXCdw> [Accessed 01 Jan 2022].
- 9 Ngwa W, Irabor OC, Schoenfeld JD, et al. Using immunotherapy to boost the abscopal effect. *Nat Rev Cancer* 2018;18:313–22.
- 10 Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *Science* 2020;367. doi:10.1126/science.aax0182. [Epub ahead of print: 31 01 2020].
- 11 Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017;18:312–22.
- 12 Raggi D, Miceli R, Sonpavde G, et al. Second-Line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. *Ann Oncol* 2016;27:49–61.
- 13 Grass GD, Krishna N, Kim S. The immune mechanisms of abscopal effect in radiation therapy. *Curr Probl Cancer* 2016;40:10–24.
- 14 Wu C-T, Chen W-C, Chang Y-H, et al. The role of PD-L1 in the radiation response and clinical outcome for bladder cancer. *Sci Rep* 2016;6:19740.
- 15 Magalhães DST, Magalhães HM, Mesquita ASA. Long lasting complete response with immunotherapy in a metastatic bladder carcinoma: a case report. *Porto Biomed* 2021;6:e127.
- 16 Bonfante G, Fantinel E, Masini C, et al. Exceptional response to immunotherapy in association with radiotherapy in patient with breast metastasis from urothelial carcinoma: A case report. *Urol Case Rep* 2021;34:101444.
- 17 Demaria S, Golden EB, Formenti SC. Role of local radiation therapy in cancer immunotherapy. *JAMA Oncol* 2015;1:1325–32.
- 18 Dietrich B, Siefker-Radtke AO, Srinivas S, et al. Systemic therapy for advanced urothelial carcinoma: current standards and treatment considerations. *Am Soc Clin Oncol Educ Book* 2018;38:342–53.
- 19 Daro-Faye M, Kassouf W, Souhami L, et al. Combined radiotherapy and immunotherapy in urothelial bladder cancer: harnessing the full potential of the anti-tumor immune response. *World J Urol* 2021;39:1331–43.
- 20 Walshaw RC, Honeychurch J, Illidge TM, et al. The anti-PD-1 era - an opportunity to enhance radiotherapy for patients with bladder cancer. *Nat Rev Urol* 2018;15:251–9.
- 21 Peng M, Xiao D, Bu Y, et al. Novel combination therapies for the treatment of bladder cancer. *Front Oncol* 2020;10:539527.
- 22 Galsky MD, Arjia José Ángel Arranz, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2020;395:1547–57.
- 23 Alva A, Csószai T, Ozguroglu M, et al. LBA23 pembrolizumab (P) combined with chemotherapy (C) vs C alone as first-line (1L) therapy for advanced urothelial carcinoma (UC): KEYNOTE-361. *Ann Oncol* 2020;31:S1155.
- 24 Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (Danube): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2020;21:1574–88.
- 25 Bellmunt J, Powles T, Vogelzang NJ. A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: the future is now. *Cancer Treat Rev* 2017;54:58–67.
- 26 Marron TU, Ryan AE, Reddy SM, et al. Considerations for treatment duration in responders to immune checkpoint inhibitors. *J Immunother Cancer* 2021;9:e001901.
- 27 Gajaj Levra M, Cotté F-E, Corre R, et al. Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: a national data base analysis. *Lung Cancer* 2020;140:99–106.

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