კლინიკური შემთხვევა

CHALLENGES AND MANAGEMENT OF METASTATIC CLEAR CELL RENAL CELL CARCINOMA COMPLICATED BY IMMUNOTHERAPY-ASSOCIATED PANCREATITIS AND PERICARDITIS: A CASE DISCUSSION

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Renal cell carcinoma (RCC) represents a significant burden worldwide, with a substantial proportion of patients presenting with metastatic disease at diagnosis or developing metastases after initial treatment. Conventional therapies have shown limited efficacy, prompting the exploration of novel treatment approaches. In recent years, the combination of immune checkpoint inhibitors and vascular endothelial growth factor receptor (VEGFR) inhibitors has emerged as a promising strategy for advanced RCC. However, this therapeutic regimen is not without challenges, including immune-related adverse events such as pericarditis and pancreatitis, which require careful management to ensure treatment continuation and optimal patient outcomes. Here, we present a case of a 63-year-old male with metastatic clear cell RCC who experienced immune-associated pericarditis and Grade 3 pancreatitis during systemic combination treatment with pembrolizumab and axitinib. Despite these complications, the patient demonstrated a partial response to therapy, highlighting the potential efficacy of this novel treatment approach. This case underscores the importance of personalized treatment strategies and multidisciplinary management in navigating the complexities of metastatic RCC while optimizing patient outcomes

Key words: renal cell carcinoma, vascular endothelial growth factor receptor, inhibitors

Each year, there are an estimated 403 300 new cases of renal cell carcinoma (RCC) worldwide, resulting in 175 100 deaths (1). Approximately one third of RCC patients present with metastatic disease at their initial diagnosis and 30–40% of patients with localized tumors will develop metastases after surgery(2). RCC is often resistant to conventional therapy regimens such as chemotherapy and radiotherapy (3).

During the past several years, multiple vascular endothelial growth factor receptor inhibitors (VEGFR targeted inhibitors) have become available for the treatment of advanced RCC. However, these antiangiogenic targeted agents are palliative treatments and rarely produce durable disease control. Nowadays, the combination of targeted agents (axitinib) and anti-PD1 antibody (pembrolizumab) have shown significantly longer overall survival (OS) and progression-free survival (PFS) in patients with mRCC as compared with a single targeted agent (sunitinib). This might indicate that the combination of targeted agents and immunotherapy can be a novel therapeutic regimen for mRCC(metastatic renal cell carcinoma) (4).

It is hypothesized that axitinib, a more selective VEGF inhibitor than others previously tested, could be combined safely with pembrolizumab (anti-PD-1) and yield antitumour activity in patients with treatment-naive advanced renal cell carcinoma(5) .

However, treatment success can be reduced by adverse immune activation events, which is not observed with classical cytotoxic agents. This overactivation can potentially affect multiple organ systems, including the gastrointestinal tract, endocrine system, liver, lungs, nervous system, skin, and pancreas. In a previous review of toxicities of immune checkpoint inhibitor therapy, grade 2–4 pancreatitis, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.1, was reported in nearly 1.8% of patients who received nivolumab or pembrolizumab (6) .

According to the literature ICI-related pancreatitis can present similarly to traditional acute pancreatitis but may have atypical features. It is graded from I to V based on the severity of elevation in amylase or lipase levels. Imaging features are nonspecific and can mimic autoimmune and chronic pancreatitis.

For asymptomatic elevation of lipase or amylase (grade I), immunotherapy can continue with close monitoring. Symptomatic cases (grade II) require discontinuation of immunotherapy and corticosteroid treatment. For more severe cases (grade III-IV), higher doses of corticosteroids are indicated, and immunotherapy should be permanently discontinued. Rechallenge strategies depend on various factors including tumor status, patient preference, and risk of recurring immune-related adverse events (irAEs)(9).

Among patients with cancer, pericardial effusions often occur due to the cancer itself, but may also develop secondary to treatment with traditional cytotoxic chemotherapy, radiation therapy, or targeted therapies (7).

Myocarditis is the most commonly described cardiac toxicity with ICI use .There are limited data on the occur-

rence, associations and outcomes of pericardial effusions and pericarditis on or after treatment with immune checkpoint inhibitors (ICIs)(8).

Numerous case reports have documented instances of pericardial effusion or tamponade in individuals undergoing treatment with immune checkpoint inhibitors . While the precise mechanisms behind these cardiac immune-related adverse events remain unclear, various theories have been proposed. One such theory suggests that ICIs may interfere with the negative regulators of immune activation, leading to a breakdown in the peripheral tolerance of self-reactive T cells.

Corticosteroids are commonly employed to manage irAEs, particularly those classified as grade 3 or 4, and sometimes grade 2. These medications work by suppressing immune activation through both transcriptional and non-transcriptional pathways. Despite their widespread use in treating irAEs, it's noteworthy that prior corticosteroid use has been associated with an increased risk of subsequent pericardial disease, potentially due to the known tendency for corticosteroids to exacerbate or trigger non-ICI-related pericarditis (10).

Hereby we present a case of a 63-year-old man diagnosed with right kidney cancer in 2015, at which time surgery—a partial nephrectomy—was performed. In 2022, he began experiencing back pain. Radiological studies revealed left kidney cancer and metastases in the right lung, chest walls, and bones. A biopsy taken from the metastatic site in the soft tissues of the back and chest area confirmed metastasis of clear cell renal cell carcinoma. The patient was deemed a candidate for systemic combination treatment according to the following protocol: pembrolizumab (Brand Name KEYTRUDA) administered at 2 mg/kg every 3 weeks in combination with axitinib (Brand Name INLYTA) at a dosage of 5 mg twice daily. This treatment regimen was initiated in December 2022.

Following the fifteenth cycle of immunotherapy, the patient reported complaints of dry cough and positional chest pain. Investigative studies (TTE, CMRI) confirmed a diagnosis of immune-associated pericarditis, which was managed with steroid treatment, specifically methylprednisolone. Despite the occurrence of pericarditis, anticancer treatment was not halted. Subsequently, the patient developed Grade 3 pancreatitis (which was diagnosed by 3 times lipase and 5 times amylase elevation), which was also managed with steroids

The case presented highlights a complex scenario of metastatic clear cell renal cell carcinoma (RCC) in a 63-year-old male patient. Despite undergoing partial nephrectomy in 2015 for right kidney cancer, the disease progressed to metastatic lesions in various sites by 2022, including the left kidney, right lung, chest walls, and bones. The patient was initiated on systemic combination treatment with pembrolizumab and axitinib as per the standard protocol

The subsequent development of immune-associated pericarditis and Grade 3 pancreatitis during the course of treatment introduced significant challenges in managing the patient's condition. Pericarditis, a rare immune-related adverse event associated with immune checkpoint inhibitors like pembrolizumab, necessitated prompt intervention with steroid therapy, specifically methylprednisolone. Despite these complications, the decision to continue anticancer treatment was made, highlighting the delicate balance between managing adverse events and maintaining therapeutic efficacy.

The assessment of partial response to anticancer treatment indicates some degree of tumor control, albeit not complete eradication. This outcome underscores the heterogeneous nature of RCC and the need for personalized treatment strategies tailored to individual patient characteristics and disease biology. Additionally, the patient's satisfactory condition and stable disease suggest a favorable response to therapy despite the encountered challenges.

Moving forward, close monitoring and multidisciplinary management involving oncologists, cardiologists, surgeons and gastroenterologists will be crucial in optimizing the patient's treatment outcomes while mitigating the risk of further complications.

ლიტერატურა:

References:

1. *Ferlay J, Colombet M, Soerjomataram I et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019; 144: 1941–1953*
2. *Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008; 34: 193–205.*
3. *Rini BI. Metastatic renal cell carcinoma: many treatment options, one patient. J Clin Oncol 2009; 27: 3225–3234)*
4. *Tamaki Kakuwa, Masao Hashimoto, Atsuko Izumi, Go Naka, Yuichiro Takeda, Haruhito Sugiyama Pembrolizumab-related_pancreatitis_with_elevation_of pancreatic tumour markers.DOI: 10.1002/rcr2.525 Publish Year: 2020 Publication: Respirol Case Rep. 2020 Mar; 8(2)*
5. *Prof Michael B Atkins MD , Elizabeth R Plimack MD , Prof Igor Puzanov MD , Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial - The Lancet Oncology Volume 19, Issue 3, March 2018, Pages 405-415*
6. *Hofmann L, Forschner A, Loquai C, et al. 2016. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side effects of anti-PD-1 therapy. Eur. J. Cancer 60:190–209*
7. *1. Adler Y, Charron P, Imazio M, et al.. 2015 ESC guidelines for the diagnosis and management of pericardial diseases. Rev Esp Cardiol 2015;68:1126. 10.1016/j.rec.2015.10.008*

8. Altan M, Toki MI, Gettinger SN, et al.. Immune checkpoint inhibitor-associated pericarditis. J Thorac Oncol 2019;14:1102–8. 10.1016/j.jtho.2019.02.026
9. Sjoerd Kramer,* Koen van Hee,† Hans Blokzijl, Immune Checkpoint Inhibitor-related Pancreatitis: A Case Series, Review of the Literature and an Expert Opinion . JOURNAL OF IMMUNOTHERAPY (HAGERSTOWN, MD. : 1997) J Immunother. 2023 Sep; 46(7): 271–275.
10. Jingyi Gong,Zsofia Dora Drobni, Amna Zafar, Pericardial disease in patients treated with immune checkpoint inhibitors. J Immunother Cancer. 2021; 9(6): e002771.

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