Immune-related cystitis due to immune checkpoint inhibitors: a case report

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Case Report

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Abstract

**Background**: Immune checkpoint inhibitors (ICIs) have been proven to be beneficial in multiple advanced malignancies. However, the widespread use of ICIs also occurred with various immune-related adverse events (irAEs). However, while various immune-related adverse events related to immune checkpoint inhibitors have been reported, there are few reports of lower urinary tract symptoms.

**Case presentation**: A 42-year-old woman with lung cancer who was being treated with sintilimab, anlotinib, and denosumab presented to the nephrology department with frequent micturition, urgency, odynuria and gross hematuria. Initial laboratory tests did not reveal bacteria, but CT examination suggested cystitis. After empiric antiinfective therapy, the above symptoms did not improve significantly. The patient stopped taking sintilimab and completed cystoscopy. Based on the combined clinical manifestations and laboratory findings, he was diagnosed with immune-related cystitis. Symptomatic relief was achieved via steroid treatment. Thereafter, the patient has been followed for 3 months without any symptoms or recurrence of immune-related cystitis.

**Conclusions**: immune-related cystitis is a commonly misdiagnosed disease. However, early diagnosis, treatment and prophylaxis through accumulated clinical data can help patients achieve a good prognosis. Therefore, clinicians need to be well aware of the variety of clinical characteristics and treatment options of this disease.

Introduction

The appearance of immune checkpoint inhibitors (ICIs) is of epoch-making significance in oncology. The application of ICIs significantly prolongs the survival time of patients and is widely used in clinical practice. With the wide application of ICIs, immune-related adverse events (irAEs) have been gradually reported. This article reports a case of immune-related cystitis after sintilizumab, anlotinib and denosumab immunotherapy to provide reference for clinical treatment.

Case Report

A 42-year-old female patient visited The First College of Clinical Medical Science, China Three Gorges University in October 2019 with multiple nodules on the left neck, irritable dry cough and headache. The patient was diagnosed with "malignant tumor of the right lung" and admitted to hospital for treatment. After receiving multi-line treatment, including chemotherapy, and targeted therapy, among others, the effect was not good and the patient's disease progressed. On April 26, 2022, the patient was treated with Sintilimab, Anlotinib and Denosumab, a few days The patient experienced gross hematuria with frequent micturition, urgency and odynuria. She did not receive any treatment until she was re-admitted to the hospital on May 24,2022. We performed a routine urine examination, the results showed urobilinogen 2+, urine occult blood 1+, urine protein 2+, white blood cells 3+, sediment red blood cells 51.6 cells/ul. We also did a urine culture, but it didn't show any bacteria. In addition, the white blood cell count, neutrophil
count, C-reactive protein and procalcitonin were not abnormal. CT(Computed Tomography) examination of the patient's urinary system: the bladder wall is thickened, the surrounding fat space is blurred, considering inflammation (Fig. 1), diagnosis: Cystitis. At first, we considered the possibility of cystitis caused by bacteria. So, we treated the disease with amoxicillin and clavulanate potassium, 10 days later (From 25 May to 4 June), we rechecked the patient's urinalysis, the result show that occult blood 2+, white blood cells 3+, sediment red blood cells 85.9(cells/ul), sediment white blood cells 1486.2(cells/ul).

According to the examination results, it show that the treatment effect was not good. After consultation with oncologist, it was considered to be related to sinilizumab, and it was suggested to discontinue tumor drugs to complete cystoscopy. The drug was switched to Piperacillin Sodium and Tazobactam Sodium for Injection (June 5 to June 10). During this time we again urine culture, the result is still negative. The patient's symptoms of frequent micturition, urgency and odynuria were improved than before, but there's still hematuria. The reexamination results showed that occult blood 1+, white blood cell 3+, sediment red blood cell 35.8(cells/ul), sediment white blood cell 1638.2(cells/ul). In this patient with limited response to anti-infective therapy. So, we performed cystoscopy, which showed hyperemia and redness of bladder mucosa, bilateral ureteral orifices, and no neoplasm in bladder. It suggest immune-related cystitis or radiation-related cystitis (Fig. 2). Combined with the patient's urine routine, blood test, urinary CT, medication information and cystoscopy results, we considered the diagnosis of immune-related cystitis. Hormone therapy is recommended according to CTCAE grade 2 and above, so we treat it with steroids from June 11(methylprednisolone hemisuccinate 40mg, intravenous drip for 3 days). After steroid treatment the symptom of frequent micturition, urgent micturition and dysuria disappeared, and hematuria also disappear. So the patient was discharged without incident, the patient was told to change the methylprednisolone hemisuccinate to prednisolone (PSL) maintenance dose of 1.0 mg/kg and taper. Final maintenance dose was 10mg daily until 28 July 2022, the patient's re-examination of urine routine showed no abnormality, so prednisolone was discontinued(Fig. 3). During the follow-up on August 10, 2022, the urine routine of the patient remained normal.

**Discussion**

ICIs are monoclonal antibodies directed against negative regulatory components of T cells. These monoclonal antibodies work by blocking internal down-regulators of the immune system, so-called "immune checkpoints." ICIs restore the tumor-killing activity of T lymphocytes by blocking the signaling pathways of cytotoxic T lymphocyte associated antigen 4 (CTLA-4) or programmed death protein 1(PD-1) and programmed death ligand 1 (PD-L1)[1]. There are three major categories of ICIs currently used in clinical practice: CTLA-4,PD-1 and PD-L1. With the increasing use of immune checkpoint inhibitors, adverse reactions have been reported[1]. The most common adverse reactions are skin, intestinal, endocrine, pulmonary and musculoskeletal adverse reactions[2].

The mechanism of immune-related adverse reactions remains unclear. Some potential mechanisms include increased activity of T cells against antigens present on tumors and normal tissues; Increased concentration of pre-existing autoimmune antibodies; Increased levels of inflammatory cytokines; enhanced immune response mediated by components of CTLA-4 antibody directly bound to normal
tissues expressing CTLA-4 antibody[3]. It has been reported that combination therapy with immune checkpoint inhibitors may lead to an increased incidence and earlier onset of irAEs, coincidentally, this patient was treated with a combination of immune checkpoint inhibitors[4]. To our knowledge, current reports of immune-related cystitis are rare in irAEs. The patient's urine routine, urine cytology and urinary CT showed cystitis, which was ineffective after treatment with multiple anti-infective drugs, so it should not be considered as the pathogenic bacteria of urinary tract infection. The patient's urinary symptoms were improved than before when using steroid hormone, and the reexamination of urine routine showed gradual improvement, so it was considered as immune-related cystitis.

Studies have shown that steroid therapy does not affect the efficacy of immune checkpoint inhibitor therapy[5]. Treatment of irAEs of CTCAE Grade 2 or higher requires dose delay or discontinuation and symptomatic treatment. Steroids are recommended for Grade 2 irAEs and Grade 3 or higher irAEs that persist for more than 1 week[6]. This patient was CTCAE Grade 3, steroids were administered as prescribed and were gradually reduced and eventually discontinued as symptoms improved. If urinary tract irritation symptoms occur during ICIs, multiple etiological examinations have no evidence of infection, and anti-infection treatment is ineffective, it is necessary to be alert to the possibility of immune-related cystitis. In this case, the symptoms were relieved in a short time after stopping ICIs and using hormone therapy, which confirms that hormone therapy is effective for immune-related cystitis. At present, there are few case reports of immune-related cystitis, so it is impossible to further analyze the high risk factors, severity of disease, hormone treatment dose, prognostic factors and so on. We believe that these problems will be solved gradually in future research.

We reported a case of immune-related cystitis following treatment with ICIs. This case reminds us of the need to consider the possibility of irAEs for any symptoms that develop during the treatment period of ICIs. The possibility of immune-related cystitis should be considered as soon as possible when there are urinary system symptoms, urine routine, urine cytology, etc. indicating inflammatory changes, but there is no evidence of infection and tumor, and anti-infective treatment is ineffective. In addition, we need to cooperate with professional oncologists to help diagnose irAEs timely and accurately. This case also suggests that early steroid therapy may help to control the progression of immune-related cystitis and reduce the total dose and time of steroids.

**Abbreviations**

IRAE
immune-related adverse event
ICIs
immune checkpoint inhibitors
irAEs
immune-related adverse events
CT
computed tomography
CTCAE
common terminology criteria for adverse events
PSL
prednisolone
CTLA-4
cytotoxic T lymphocyte associated antigen 4
PD-1
programmed death protein 1
PD-L1
programmed death ligand 1

Declarations

Acknowledgements

Not applicable.

Authors’ contributions

WLL, KZS, XWL and PZ were involved in diagnosis, management and follow-up of the patient at all stages. CYM and YL contributed substantially and significantly to the literature review, drafting of the initial manuscript, critical revision and preparation of the final version. All authors have participated sufficiently in the work to take public responsibility for the presented content. All the authors have contributed, read and approved the final and revised version of the manuscript.

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Records and data pertaining to this case are in the patient’s secure medical records in the First College of Clinical Medical Science, China Three Gorges University. If needed, the relevant material can be provided by corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Consent for publication
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

**Availability of data and materials**

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**References**


**Figures**
Figure 1

Urinary CT: Bladder wall is thickened and the surrounding fat space is blurred.

Figure 2

Cystoscope view: hyperemia and redness of bladder mucosa, bilateral ureteral orifices, and no neoplasm in bladder.
Changes of RBCs and WBCs in patients treated with drugs. From 25 May to 4 June, we used amoxicillin and clavulanate potassium; From June 5 to June 10, we used Piperacillin Sodium and Tazobactam Sodium; From June 11 to June 15, we used steroids.

**Supplementary Files**

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