


Case Report

A case of steroid-resistant cystitis as an immune-related adverse event during treatment with nivolumab for lung cancer, which was successfully treated with infliximab

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Abbreviations & Acronyms

irAE = immune-related adverse events
NCCN = National Comprehensive Cancer Network
NRS = Numerical Rating Scale

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Introduction: Immune checkpoint inhibitors are widely used in various cancers as a standard treatment. 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: The patient was a 60-year-old man with primary lung cancer who was receiving long-term nivolumab therapy. He was referred to our department due to the sudden onset of glans penile pain and micturition pain. We suspected non-bacterial cystitis as an immune-related adverse event caused by nivolumab and were able to treat it by administering prednisolone. While his symptoms and findings on cystoscopy recurred during prednisolone therapy, we were able to treat him again by administering an additional dose of infliximab.

Conclusion: A few reports have described cases of immune checkpoint inhibitor-induced cystitis for which prednisolone was effective. This report is the first to describe cystitis as a steroid-resistant immune-related adverse event.

Key words: cystitis, immune checkpoint inhibitors, immune related adverse event, infliximab, steroid-resistant.

Keynote message

This report describes a patient who was diagnosed with cystitis as an immune-related adverse event. The cystitis was steroid-resistant, but we were able to treat it with infliximab, as with other immune-related adverse events. Such a case is extremely rare among those with lower urinary tract symptoms.

Introduction

Immune checkpoint inhibitors, such as nivolumab, are now widely used to treat various cancers. With the spread of this approach, various immune-related adverse events (irAEs) due to immune checkpoint inhibitors have been reported.^{1,2} Although various symptoms have been noted, differing from the adverse events related to conventional chemotherapy, there have been few reports of lower urinary tract symptoms as an irAE,² and there are no clear diagnostic criteria or treatment strategies. We herein report a case of non-bacterial cystitis that was considered to be an irAE and our experience with a case that was difficult to treat.

Case presentation

A 60-year-old man was undergoing chemotherapy for Stage IIIB primary lung cancer in the respiratory surgery department. After 77 courses of nivolumab, he was referred to our department for the sudden onset of glans penile pain and micturition pain. Bacterial cystitis was suspected, and levofloxacin had been administered by the main department 7 days before visiting our department; however, a urinalysis revealed pyuria at the initial visit. We suspected the cystitis to be antibiotic-resistant, so we changed the antibiotic agent after sending a urine

sample to the laboratory for culture. As he was unable to achieve symptom relief, he was admitted to our department 2 days after the first visit.

Abdominal computed tomography showed no abnormal findings in the urinary tract. Cystoscopy showed no tumors or stones in the urethra or bladder, but the bladder mucosa generally showed marked inflammatory findings (Fig.1). In addition, the findings of urine culture and urine cytology were also negative. Given the above, we suspected non-bacterial cystitis as an irAE caused by nivolumab.

As a diagnostic treatment, methylprednisolone at 60 mg/day (1 mg/kg) was started, and the symptoms and cystoscopic inflammatory findings improved immediately. Since the pyuria and symptoms remained under control even after the dose of methylprednisolone was reduced to 20 mg/day, he was discharged home while continuing methylprednisolone 20 mg/day.

However, 1 month after discharge, glans penile pain, micturition pain and pyuria recurred, and cystoscopy showed inflammatory findings in the bladder mucosa. A urine culture was again negative, as before, so we suspected recurrence of the non-bacterial cystitis as irAE. One month after discharge, we gradually increased the dose of methylprednisolone. However, the symptoms were markedly enhanced, and we had to increase the dose of methylprednisolone to 60 mg/day, 3 weeks after the recurrence of symptoms. After increasing the dose of methylprednisolone to 60 mg/day, the symptoms and pyuria improved, but it was difficult to reduce the dose of methylprednisolone below 40 mg/day considering the severity of the symptoms. Therefore, we decided to administer infliximab (5 mg/kg) in conjunction with methylprednisolone,

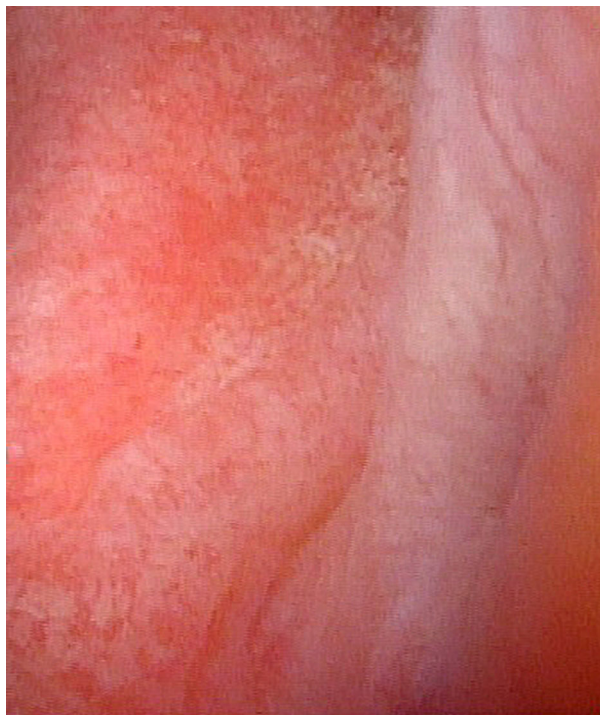


Fig. 1 Cystoscopy at the initial examination showed diffuse mucosal redness and bleeding.



Fig. 2 Cystoscopy after infliximab admission no longer showed diffuse mucosal redness or bleeding.

after consulting the medical oncologist. Two weeks after starting infliximab, the dose of methylprednisolone was reduced to 30 mg/day, and the symptoms did not recur (Fig.2). We were subsequently able to stop the administration of infliximab and decrease the dose of methylprednisolone to 20 mg/day. Four weeks passed without recurrence of symptoms even after we reduced the dose of methylprednisolone to 20 mg/day (Fig.3). Nivolumab has been discontinued since the first emergence of Non-bacterial cystitis as an irAE.

Discussion

Immune checkpoint inhibitors have become widely used, and a wide variety of irAEs have subsequently been reported.^{1,2} Among them, there have been only a few reports of lower urinary tract events as irAE, with just five cases reported, all of which were non-bacterial cystitis; no reports from overseas have been published.³⁻⁶

There is no clear diagnostic standard, so an exclusion diagnosis is necessary. Bacterial cystitis, interstitial cystitis and malignant disease are all mentioned as differential diseases. In addition, there is no clear policy regarding the treatment in the NCCN guidelines, and in all cases reported in Japan, the immune checkpoint inhibitors were withdrawn and steroids administered, as for the general treatment of irAEs.

Non-bacterial cystitis as an irAE, which has already been reported, was shown to be relieved by drug suspension and steroid administration,³⁻⁶ but there have been no reports of cases such as the present one, in which recurrence occurred after steroid administration and treatment was difficult even when steroid administration was again performed. There have

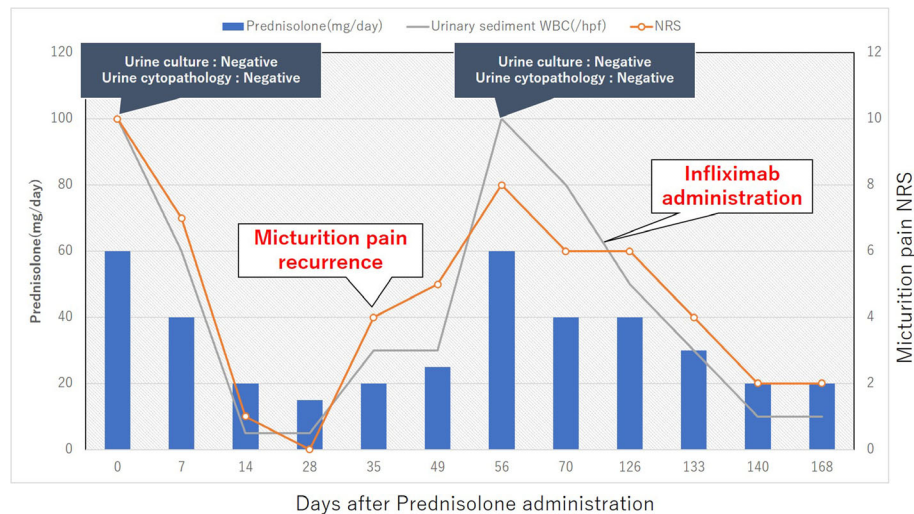


Fig. 3 Progress after initiation of steroid administration.

been reports of irAEs that were difficult to treat involving colitis and interstitial pneumonia, and the NCCN guidelines recommend the use of infliximab as a treatment in such cases.⁷ In the present case as well, immunosuppressive therapy with methylprednisolone alone made it difficult to control the symptoms, but the combined use of infliximab was able to improve the symptoms and gradually allow us to reduce the methylprednisolone dose.

When performing immunosuppressive therapy for irAE, it is important to perform careful consultation with the disease-specific department. In this example, the department corresponding to the symptom was our own department, but since we lack much experience using immunosuppressive drugs, immunosuppressive therapy was performed in consultation with the oncology department.

In addition, it is recommended that the period for tapering steroids be set at 4 weeks or longer, with 6 to 8 weeks or longer advised in some cases.⁷ With the long-term use of steroids, it is necessary to prevent adverse events such as infection and osteoporosis, and consulting with a department that has a lot of experience with immunosuppressive drugs is recommended.

In conclusion, there have been several reports of cases of immune checkpoint inhibitor-induced cystitis that were effectively treated with methylprednisolone. This report is the first to describe cystitis as a steroid-resistant irAE. Symptoms of steroid-resistant cystitis were relieved early by concomitant use of infliximab.

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Author contributions

Hiroyuki Fukunaga: Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. Kenta Sumii: Conceptualization; formal analysis; writing – review and editing. Shun Kawamura: Validation. Masato

Okuno: Validation. Isao Taguchi: Validation. Gaku Kawabata: Writing – review and editing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Approval of the research protocol by an Institutional Review Board

This study was approved by the Institutional Review Board of Kansai Rosai Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki. All specimens were collected from the patients after written consent was obtained.

Registry and the Registration No. of the study/trial

Not applicable.

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