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Nivolumab-Induced Severe Akathisia in an Advanced Lung Cancer Patient

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 58
Final Diagnosis: Nivolumab induced severe akathisia
Symptoms: Distress fidgety • restlessness
Medication: —
Clinical Procedure: Methylprednisolone pulse therapy and other drugs
Specialty: Oncology

Objective: Adverse events of drug therapy

Background: Nivolumab is an anti-PD-1 immune checkpoint inhibitor that was recently developed for cancer immunotherapy. In the clinical trials of nivolumab, its adverse effects were reported to be less likely than those of conventional anti-cancer agents; however, after practical clinical distribution, it has come to be known that nivolumab induces various immune-related adverse events.

Case Report: A 58-year-old male with a recurrence of lung adenocarcinoma was treated with nivolumab. Only four days after the initial administration of nivolumab, the patient presented with unbearable restlessness and distress that was resistant to all therapeutic agents used, and it gradually became worse. He finally came to need deep sedation despite his cancer status being stable during the course. Clinical tests including magnetic resonance imaging, cerebrospinal fluid cytology, and antibodies of paraneoplastic syndrome exhibited no signs of encephalitis or another possible cause of the neuropathy. The diagnosis of akathisia could be made only by his somatoform presentation. It was uncertain whether or not this complication was correlated with the activation of his immune system.

Conclusions: Anti-immune check point inhibitors may induce many unknown adverse events. Severe akathisia induced by nivolumab, as in our case, has not been reported yet. Collecting every adverse event of nivolumab may be important to make a better algorithm to manage its huge variety of complications.

MeSH Keywords: Akathisia, Drug-Induced • Antineoplastic Agents • Carcinoma, Non-Small-Cell Lung

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/900941

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Background

Nivolumab is an anti-PD-1 immune checkpoint inhibitor antibody that disrupts cytotoxic lymphocytes' surface receptor PD-1 mediated immune tolerance to the cancer cells. Anticancer effects of nivolumab have been reported as outstanding [1–3], and its application has been rapidly extended for many types of cancers.

In the clinical trials of nivolumab [1–3], its adverse effects were reported to be less severe than those of conventional anticancer agents; however, since its clinical use has been started, it has come to be known that nivolumab induces various types of immune-related adverse effects. Herein, we describe the first report of severe akathisia induced by nivolumab in an advanced non-small cell lung cancer patient.

Case Report

A 58-year-old male with a recurrence of lung adenocarcinoma was treated with nivolumab. Just 4 days after the first administration of nivolumab (150 mg/body), he had unbearably irritated feelings and felt fidgety. Two more nivolumab infusions every 2 weeks were added before nivolumab was discontinued due to the progress of his symptoms. Finally nivolumab-induced akathisia was suspected. Typical "rocking from foot to foot when standing" was absent, but an intermittent compulsion to move and pacing up and down were observed. Initially, the symptoms occurred once or twice daily in fits, but the repetition increased gradually.

We performed several examinations to make a diagnosis, but these failed to reveal a cause. Magnetic resonance imaging of his brain exhibited no findings of encephalitis or cancer metastasis. His cerebrospinal fluid demonstrated normal pressure and normal features with no cytological evidence of cancer dissemination. Twelve antibodies of paraneoplastic neurologic syndrome were comprehensively tested: amphiphysin, CV2, PNMA2(Ma2/Ta), Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, and Tr/DNER. However, the tests were negative for all of them.

We consulted both a psychiatric physician and a neuro-physician; however, they had different opinions about the diagnosis. The psychiatric physician said that the patient's symptoms were consistent with akathisia, whereas the neuro-physician said that it was less likely to be akathisia but a kind of somatoform mental reaction to the cancer therapy. Actually, the patient's mental status had been very stable for the 5 years of his lung cancer treatment, even after he had a relapse of his disease 3 years before, and we favored the psychiatric physician's opinion.

When the symptoms worsened, he hardly communicated and made compulsive sequential movements that he repeated endlessly. Those were as follows: first, he lay on the bed with a moan; next, he stood up and moved to the door; then, he moved back to the bed. Regarding the akathisia rating scale [4], his symptoms were rated 4 or 5 (the maximum rating was 5) during the attack phases, which occurred inconsistently at any hour of the day or night. Even when he seemed to be staying calm, the rating was 1 or 2.

Fifty milligrams of prednisolone was given for possible immune-related encephalitis. Some other drugs such as biperiden hydrochloride, alprazolam, and diazepam were used to treat the akathisia. However, once the attack had occurred, in spite of the usage of those agents, it continued until sedative drugs like an intravenous bolus of diazepam or hydroxyzine pamoate were used.

Therapy with neuroleptic agents such as haloperidol, chlorpromazine, risperidone, and quetiapine was also attempted, but we found all of them ineffective. Phenytoin was also used for possible epilepsy, although it was not effective. In the end, one more methylprednisolone pulse therapy failed to relieve his symptoms.

Ultimately, after contracting interstitial pneumonia coincidently, he came to need deep sedation to reduce his pain four months after the first usage of nivolumab. His cancer status was stable during the course.

Discussion

Nibolumab's mechanism for inhibiting cancer progression is as follows: when the programmed death 1 (PD-1) receptor on activated T-cells binds to its ligand PD-L1 on cancer cells, T-cell activation is disrupted and the tumor escapes immunity. Nivolumab is a PD-1 antagonist that inhibits the PD-L1-PD-1 anti-immune pathway and restores the immune response of the cytotoxic T-cells [5].

Although adverse effects of nivolumab were reported to be less likely in the clinical trials, many immune-related adverse events occurred as many patients have come to be exposed to nivolumab. For instance, interstitial lung disease, thyroiditis, type I diabetes mellitus, colitis, encephalitis, myositis, myasthenia gravis, dermatitis, hepatitis, and all the inflammatory disorders can occur in every segment of the whole body.

Of those, autoimmune encephalitis [6] and Guillain-Barré syndrome [7] have been reported as nivolumab-induced neuropathy; however, up of now, akathisia or akathisia-like neuropathy has not been reported. Symptoms experienced by our patient

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were so severe that we could hardly manage them, and we could not identify effective drugs to control them. Recently, Tanaka et al. [7] reported the efficacy of intravenous immunoglobulin administration, with which we did not challenge our patient, for nivolumab-induced Guillain-Barré syndrome.

Conclusions

Severe akathisia as an adverse event of nivolumab therapy, as in our case, has not been reported yet. Anti-immune check point inhibitors may induce many unknown adverse events, and those would become potential limiting factors in the practical usage of these agents. Collecting every adverse effect of nivolumab is warranted to make a better algorithm to manage its huge variety of complications.

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Conflict of interest statement

No conflicts of interest.

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Ethical approval

This publication was approved by the ethical board of the Miyagi Cancer Centre: the reference number is #2885.

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