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Risk of immunotherapy-related narcolepsy in genetically predisposed patients: a case report of narcolepsy after administration of pembrolizumab

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ABSTRACT

Background Immune-related adverse events associated with immune checkpoint therapy cause autoimmune disease-like symptoms. People who carry specific genotypes or haplotypes of human leucocyte antigen (HLA) are known to be predisposed to develop autoimmune diseases including narcolepsy. Immunotherapy could be a trigger to develop narcolepsy in predisposing HLA positive patients.

Case presentation A 66-year-old woman with stage IVB endometrial carcinosarcoma experienced daytime sleepiness and temporary muscle weakness 14 days after the administration of an immune checkpoint inhibitor, pembrolizumab. These were consistent with the main symptoms of narcolepsy with cataplexy. This patient carried a highly predisposing HLA haplotype for narcolepsy; HLA-DQB1*06:02, DRB1*15:01, DQA1*01:02 and DRB5*01:01:01. A hypocretin-1/orexin-A concentration in the patient's cerebrospinal fluid was low at 9.6 pg/mL in ELISA, and 155.5 pg/mL in radioimmunoassay that was below the normal level of 200 pg/mL. Therefore, she was diagnosed with narcolepsy tentatively according to the International Classification of Sleep Disorders, third edition diagnostic criteria for narcolepsy. The onset of narcolepsy in the 60s is very rare, and narcoleptic symptoms in our patient were likely to be caused by pembrolizumab.

Conclusions This case suggests that treatment with immune checkpoint inhibitors potentially causes narcolepsy in genetically predisposed patients.

INTRODUCTION

Immunotherapy using immune checkpoint inhibitors has recently been a promising new treatment showing remarkable benefit in a range of advanced cancers. The immune checkpoint inhibitors treat cancers by activating the human immune system that controls immune response toward cancer cells. Pembrolizumab, one of the immune checkpoint inhibitors blocks PD-1, an immune check point protein and demonstrated antitumor activity; objective response rate of 34.3% (95% CI 28.3% to 40.8%) in patients with cancer with microsatellite instability (MSI)-high.[1] However, the activated human immune system also attacks healthy cells, causing ≥grade 3 adverse events in about half of treated patients with immune checkpoint inhibitors or any grade adverse events in about 100%.[2] These adverse events are called immune-related adverse events (irAEs) and their symptoms are similar to those of autoimmune diseases (eg, ulcerative colitis, thyroiditis, interstitial pneumonia and type 1 diabetes mellitus).[3] Some irAEs including colitis and pruritus were recently reported to be associated with specific genotypes of human leucocyte antigen (HLA).[4] HLAs are polymorphic cell-surface proteins, and combination of HLAs is unique to each individual, serving as a landmark of self cells. Many autoimmune diseases are known to be associated with specific HLA genotypes or haplotypes; HLA-DRB1*04:05 for rheumatoid arthritis,[5] DQA1*05:01 and DQB1*03:02 for type 1 diabetes,[6] and HLA-DRB1*01:03 for ulcerative colitis. People carrying HLA B27 develop ankylosing spondylitis with a greater OR 171 compared with healthy controls.[7] The genotype of HLA-DQB1*06:02 confers increased risk of developing narcolepsy with extraordinary OR 251.[8]

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucination. The onset occurs mostly between the age of 10 and 50 years, especially teenage years.[9 10] Narcolepsy had long been suspected as an autoimmune disease because of the association with the specific HLA genotypes and haplotypes. Epidemiological observation recently suggested Pandemrix H1N1 influenza vaccination is one of the triggers for narcolepsy.[11] After Pandemrix H1N1 influenza vaccination, 96.8% of patients who

developed narcolepsy were found to carry a haplotype in the HLA-DRB5*01:01:01, DRB1*15:01, DQA1*01:02, DQB1*06:02 compared with 28.0% of general population controls ($p=6.17\times10^{-16}$).[12] For development of narcolepsy, in addition to genetic predisposition, environmental factors such as vaccination is likely required. In most patients, narcolepsy results from a loss of hypocretin neurons in the lateral hypothalamus. Hypocretin-1/orexin-A neuron specific CD4+ and CD8+T cells were found in the blood and cerebrospinal fluid (CSF) of patients with narcolepsy.[13 14] These studies support the autoimmune hypothesis of narcolepsy, which develops on the background of genetic predisposition.

Although there are many cases of irAEs resembling autoimmune diseases with defined specific HLA genotypes, there have been no case reports of irAE presenting symptoms of narcolepsy. Here, we report the first case of narcolepsy after the administration of pembrolizumab. The patient carried a highly predisposing HLA haplotype and had not developed narcolepsy before the immunotherapy. Therefore, the immunotherapy with pembrolizumab was highly suspected to have triggered the development of narcoleptic symptoms.

METHODS

Narcolepsy diagnosis

Type 1 narcolepsy meaning narcolepsy with cataplexy was diagnosed with the following criteria in the International Classification of Sleep Disorders, third edition (ICSD-3).[15] Both criteria (A) and (B) must be met for the diagnosis: (A) The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥3 months. (B) The presence of either one of the following: (1) The presence of cataplexy and a mean sleep latency of ≤8 min and two sleep-onset rapid eye movement periods on a multiple sleep latency test (MSLT). (2) CSF hypocretin-1/orexin-A concentration is either ≤110 pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay. In addition to the ICSD-3 criteria, presence of accurate cataplexy was judged with the latest criteria of cataplexy by European experts.[16]

HLA genotying

HLA genotyping was performed at HLA Foundation Laboratory, Kyoto, Japan. DNA was purified from the patient's blood with QIAamp DNA Blood Midi kit (QIAGEN). The DNA sample was sequenced by next-generation sequencing, Illumina MiSeq technology. The DNA sequence was genotyped by integrated genotyping system (Scisco Genetics). We performed the high-resolution HLA typing for HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1 and -DPB1.

Hypocretin-1/orexin-A assay

CSF of the patient was collected by a lumbar puncture, 10 days after somnolence and 4 days after cataplexy. A concentration of hypocretin-1/orexin-A in the CSF was measured with orexin-A radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals) as previously reported by International Institute for Integrative Sleep Medicine (WPI-IIIS) in the University of Tsukuba.[17] We also measured a concentration of hypocretin-1/orexin-A in the CSF with orexin-A ELISA kit (WAKO).

CASE REPORT

A 66-year-old woman presented with abdominal pain and was found to have an intrapelvic tumor with lung and peritoneal metastasis. Biopsy was performed and she was diagnosed with stage IVB endometrial carcinosarcoma, and the international federation of gynecology and obstetrics IVB. The patient had a clinical complete response after adjuvant chemotherapy, followed by abdominal total hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. However, the intrapelvic tumor relapsed and dysuria occurred. The patient received a total pelvic exenteration with ileal conduit as a salvage operation and was treated with standard chemotherapies for endometrial carcinosarcoma and carcinoma. Two episodes of febrile neutropenia occurred during the chemotherapies, which were treated with antibiotic therapy. The carcinosarcoma was classified as MSI high, and was eligible for treatment with an immune checkpoint inhibitor, pembrolizumab. Pembrolizumab at a dose of 200 mg/day was intravenously injected. The patient had the Eastern Cooperative Oncology Group Performance Status (PS) of 1 and did not have neurological symptoms, impaired consciousness or sleep-wake disorders. At 14 days postinjection, the patient developed a fever of 39°C (figure 1). CT showed an increase in the size of the pelvic tumor, but the cause of fever was not apparently identified. However, as bacteriuria was found, the cause of fever was suspected to be urinary tract infection, and the patient was treated with piperacillin/tazobactam in our hospital. At the same time, excessive daytime sleepiness and sleep attack occurred and persisted. The sleepiness was too intense to answer questions, causing disorientation or sleep even during conversation. The intensity of the sleepiness was temporarily weakened after naps or nocturnal sleep. No signs of paralysis or meningitis were observed. All electrolyte levels in the serum were normal. No medications that induce sleep were administered. Administration of vitamin B_1 could not improve the somnolence. Delirium due to neoplastic fever was suspected, and dexamethasone 6.6 mg/day was administered at 23 days postinjection. The steroid reduced the fever, however, did not improve the somnolence. During pleasant conversations with her family at the hospital, temporary muscle weakness affecting the whole body including the face occurred, and lasted for a few seconds. The patient showed her muscle weakness despite being fully conscious. Brain CT and MRI demonstrated no brain metastasis, degenerative disease or infarction. The MRI image did not show hypothalamic inflammation (figure 1). Gadolinium-enhanced MRI

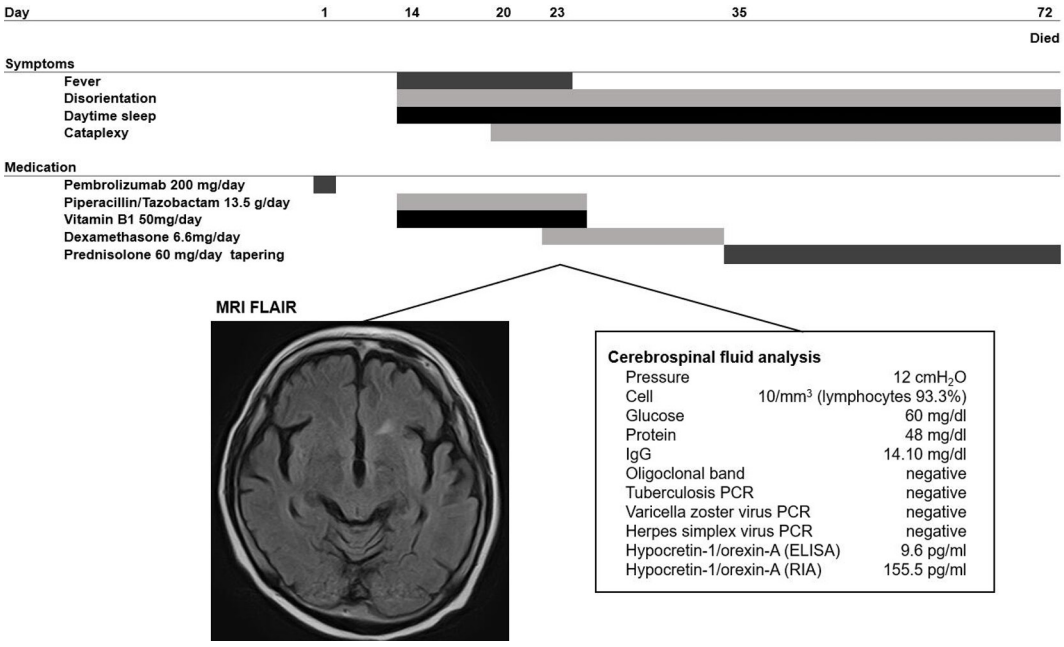

Figure 1 Clinical course, MRI and cerebrospinal fluid analysis in the patient. FLAIR, fluid-attenuated inversion recovery. RIA, radioimmunoassay.

was not performed. Surgical intervention that disrupts the blood-brain barrier had not been performed. A CSF examination showed clear fluid, normal pressure, negative oligoclonal bands, no cancer cells and no evidence of infection. The CSF revealed slightly elevated white blood cell count (10/mm^3, lymphocytes 93.3%). Serum paraneoplastic antibodies were negative (AMPH, CV2, PNMA2/Ma2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, Tr/DNER). Serum immunoglobulin G (IgG) was elevated from 1490 mg/dL at preinjection of pembrolizumab to 2091 mg/dL at postinjection, suggesting activated immune system. Autoimmune encephalitis as an irAE associated with pembrolizumab was suspected. Prednisolone 1 mg/kg was initiated and dexamethasone was discontinued at 35 days postinjection. However, the steroid treatment did not improve somnolence, disorientation or temporary muscle weakness. Pembrolizumab therapy was permanently discontinued due to the irAE, and the patient died by progression of carcinosarcoma at 72 days postinjection of pembrolizumab. Her family did not permit an autopsy.

RESULTS

The patient in the present case was initially diagnosed with an irAE encephalitis. In the clinical time course, onset of narcolepsy was suspected. Although she had no previous history of sleep-wake disorders, she repeated sleep attacks 2 weeks after administration of pembrolizumab. There were no structural disorders and no sleeping pills or opioids administered at the onset of somnolence. The latest cataplexy criteria were applied to diagnose cataplexy.[16] Among the criteria, the patient met a criterion of cataplexy with pleasant surprise when meeting a familiar acquaintance. The patient's consciousness was preserved when the loss of muscle tone of her whole body arose for a few seconds. Bilateral loss of muscle tone for a few seconds with preserved consciousness also met the cataplexy criteria. These sleep attack and cataplexy were consistent with the main symptoms of narcolepsy with cataplexy. Apparent hypnagogic hallucination and sleep paralysis were not found. The patient could not undergo polysomnography and MSLT for diagnosis of obstructive sleep apnea syndrome (OSAS) or narcolepsy due to physical weariness. Our patient did not notice snoring or apnea during sleep, we considered our case unlikely to have moderate or severe OSAS. A concentration of hypocretin-1/orexin-A in the CSF of the patient measured with RIA was 155.5 pg/mL, and that measured with ELISA was 9.6 pg/mL. This difference in the concentrations is considered to be within the range of error due to the measuring method.[18] The 155.5 pg/mL measured with RIA does not meet the narcolepsy ICSD-3 criteria (≤110 pg/mL), but is below the normal level of 200 pg/mL. One of the ICSD-3 criteria describing daytime lapses into sleep lasting for 3 months could not be applied to the present case due to short survival time, indicating inappropriateness of the criterion for patients with poor prognosis. If she had lived longer, she would have met the criterion as she had daily daytime sleep attacks. High-resolution HLA genotyping demonstrated that the patient carried HLA-DQB1*06:02, DRB1*15:01, DQA1*01:02 and DRB5*01:01:01 (table 1). In a previous report, people carrying HLA-DQB1*06:02, DRB1*15:01, DQAl*01:02 and DRB5*01:01:01 developed narcolepsy with OR 6.75 after Pandemrix influenza vaccination.[12] Almost all narcoleptic patients are known to carry HLA-DQB1*06:02, DRB1*15:01, and DQAl*01:02, regardless of race.[8 19] In particular, 100% of Japanese narcoleptic patients are reported to carry DQB1*06:02

Table 1 HLA haplotype in the patient

HLA-A		HLA-B		HLA-C							
01:01	02:01	37:01	39:01	06:02	07:02						
HLA-DRB1		**HLA-DRB5**		**HLA-DQA1**		**HLA-DQB1**		**HLA-DPA1**		**HLA-DPB1**	
10:01	15:01	01:01:01	–	01:02	01:05	05:01	06:02	01:03	–	02:01	–

HLA, human leucocyte antigen.

and DRB1*15:01.[19] These results supported that the patient's condition was similar etiology of narcolepsy with cataplexy.

DISCUSSION

Narcolepsy had long been suspected of having an autoimmune origin, because narcolepsy patients carry the haplotype HLA-DQB1*06:02, DRB1*15 and DQA1*01:02 with significantly higher rates (54.3%–100%) compared with healthy controls (12.2%–23.3%) in any race.[19] Pandemrix H1N1 influenza vaccination is epidemiologically confirmed to increase the incidence of narcolepsy.[11] Hypocretin-1/orexin-A producing neuron specific CD4+ and CD8+T cells were found in the CSF of narcolepsy patients.[13 14] These T cells are considered to attack the neurons and to be responsible for low concentration of hypocretin-1/orexin-A. An accumulation of studies revealed that narcolepsy is an autoimmune disease and a genetically predisposed disease. However, 25%–31% of genetically identical monozygotic twins are concordant for narcolepsy.[20] This finding supports the hypothesis that in addition to the genetic predisposition, a non-genetic trigger is required for the onset of narcolepsy.

We experienced a case of narcolepsy after the initiation of a PD-1 inhibitor, pembrolizumab. The patient had a highly predisposing HLA haplotype for narcolepsy. Although the narcolepsy simultaneously developed with fever, the fever itself is not thought to be the trigger of this disorder. Two episodes of febrile neutropenia before the administration of pembrolizumab did not cause narcolepsy. There were no episodes that seemed to trigger narcolepsy other than the administration of pembrolizumab. Considering that the incidence of narcolepsy in the 60s is almost zero per cent,[9] the immune checkpoint inhibitor, pembrolizumab is highly suspected to have induced narcolepsy in the 66-year-old patient in the current case. Since pembrolizumab causes irAEs similar to autoimmune diseases, pembrolizumab probably could cause an irAE similar to narcolepsy. Approximately 5.6% of the Japanese population carry predisposing HLA haplotypes for narcolepsy: HLA-DQB1*06:02, DRB1*15:01 and DQA1*01:02,[21] while the prevalence of narcolepsy is about 0.16%–0.18%.[20] This low prevalence of narcolepsy compared with the prevalence rate of predisposed HLA haplotype indicates the necessity of triggers to develop narcolepsy. Our case implies that inhibition of immune checkpoint could be a potential pathogenesis of narcolepsy. However, there have been no reports of narcolepsy as an irAE, despite the fact that many cancer patients have been treated with immune checkpoint inhibitors.[22] There are some cases of encephalitis as an irAE, some of which presented with somnolence or sleepiness.[23] Of these irAE encephalitis cases with somnolence, there may have been cases of undiagnosed narcolepsy. Anti-PNMA2/Ma2-associated encephalitis after initiation of immune checkpoint inhibitors has been reported with increased frequency.[24] In those cases, serum anti-PNMA2/Ma2 antibody levels increased. However, there was no increase in anti-PNMA2/Ma2 antibody levels in serum of our patient, therefore we thought that anti-PNMA2/Ma2-associated encephalitis was unlikely. Although typical irAE encephalitis responds well to steroid treatment, followed by symptom improvement, our case did not.

Our patient could not live a life that she had before the onset of narcolepsy due to severe somnolence. We should focus on the development of immunotherapy-related narcolepsy as that remarkably interferes with patients' daily life. Some HLA genotypes or haplotypes associated with the development of irAEs have been reported.[4] HLA haplotypes could be predictive markers for irAE narcolepsy.

Finally, we note that our report did not prove a statistical association between immune checkpoint inhibitors and narcolepsy. Etiological or biological studies are needed. In addition, there still remains the question of different concentrations of hypocretin-1/orexin-A in different measuring methods. ELISA (WAKO) recognizes two epitopes of hypocretin-1/orexin-A, and likely detect intact hypocretin-1/orexin-A.[18] However, RIA (Phoenix Pharmaceuticals) recognizes only a single epitope, and is known to detect the degradation product of hypocretin-1/orexin-A.[25] Detection of metabolites of hypocretin-1/orexin-A may mask the possible decline in real hypocretin-1/orexin-A level. The value of 155.5 pg/mL measured with RIA was lower than 200 pg/mL of normal hypocretin-1/orexin-A cut-off level, which suggested that low concentrations of hypocretin-1/orexin-A may have affected the pathology of the patients. Usually, the diagnosis of narcolepsy often needs at least several months after the onset of symptoms. In this case, the timing of lumbar puncture was very close to the onset of somnolence (10 days) and cataplexy (4 days). Therefore, some possibility exists that hypocretin-1/orexin-A neurons were damaged, but hypocretin-1/orexin-A remained from the

onset until the lumbar puncture. Current diagnostics for narcolepsy requiring long disease duration may be unsuitable to diagnose narcolepsy of irAE.

We reported the first case of narcolepsy as an irAE after the administration of an immune checkpoint inhibitor, pembrolizumab. Immune checkpoint inhibitors potentially cause irAE narcolepsy. Our patient carried a predisposing HLA haplotype for narcolepsy, indicating that we should carefully monitor patients genetically predisposed to narcolepsy when treating them with immunotherapy. The present case will hopefully alert the occurrence of irAE narcolepsy and help elucidating the mechanism of narcolepsy onset.

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Contributors YN treated the case, performed experiments, and YN and SS wrote the manuscript. ES, SS and SF treated the case. All authors discussed the results, and read and approved the final manuscript.

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Competing interests SS reports grants and personal fees (lecture fee) from Chugai, grants and personal fees from Kyowa Kirin, grants and personal fees from Eli lilly, grants and personal fees from Astra Zeneca, personal fees from Pfizer, personal fees from MSD, grants and personal fees from Novartis, grants and personal fees from Eisai, grants and personal fees from Takeda and grants from Taiho, outside the submitted work. ET reports grants from Eli lilly, personal fees from Chugai, personal fees from Pfizer, personal fees from Novartis, outside the submitted work.

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