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Abdominal pain as an initial symptom of isolated ACTH deficiency induced by nivolumab in a patient with malignant mesothelioma

Koichi Hata ,[1] Chikara Sakaguchi,[2] Michiko Tsuchiya,[2] Yukio Nagasaka[3]

[1]Department of Internal Medicine, Rakuwakai Otowa Hospital, Kyoto, Japan
[2]Department of Respiratory Medicine, Rakuwakai Otowa Hospital, Kyoto, Japan
[3]Kyoto Respiratory Center, Rakuwakai Otowa Hospital, Kyoto, Japan

Correspondence to
Dr Koichi Hata;
h-hata@koto.kpu-m.ac.jp

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SUMMARY

Used for a wide range of cancers, nivolumab has been reported to cause immune-related adverse events, including isolated adrenocorticotropic hormone deficiency (IAD). We report an 81-year-old woman with malignant mesothelioma who presented with abdominal pain after eight courses of nivolumab therapy, leading to the diagnosis of nivolumab-induced IAD. We should consider adrenal insufficiency (AI) when a patient on nivolumab complains of abdominal pain and has no other explanatory findings. Infusion-resistant hypotension and hyponatraemia can further suggest AI.

BACKGROUND

Nivolumab, an antibody that targets programmed cell death 1, is an immune checkpoint inhibitor (ICI) that has been used for a wide range of cancers.[1–3] Despite superior clinical activity to chemotherapeutic agents, ICIs have been increasingly reported to cause various types of immune-related adverse events (irAEs).[2 4–7]

Isolated adrenocorticotropic hormone (ACTH) deficiency (IAD), a rare disorder categorised as secondary adrenal insufficiency (AI), has been reported as an irAE caused by ICIs. The symptoms of IAD, such as general fatigue, anorexia, weight loss and nausea, are non-specific, which may delay diagnosis.[8] Here, we report nivolumab-induced IAD in a patient with malignant mesothelioma who had abdominal pain as an initial symptom.

CASE PRESENTATION

An 81-year-old woman with a history of Graves' disease, treated with both levothyroxine 50 µg and thiamazole 5 mg, was diagnosed with stage IIIB malignant mesothelioma in 2017. She underwent chemotherapy with carboplatin and pemetrexed for 10 courses. As disease progression was observed during chemotherapy, nivolumab (240 mg every 2 weeks) was initiated in October 2018. In January 2019, after the eighth course of nivolumab treatment, the patient underwent laparoscopic sigmoid colectomy for sigmoid colon cancer. During the perioperative period, nivolumab administration was continued. Just after the surgery, she noted mild intermittent abdominal pain, which continued for 2 months. An abdominal CT scan was performed but showed no causative abnormalities, even at the surgical sites. Two weeks later, just after the 12th course of nivolumab, the patient visited an emergency department and complained of worse abdominal pain and general fatigue.

On physical examination, her level of consciousness was normal, and her vital signs were as follows: blood pressure 88/77 mm Hg, pulse rate 115 beats per minute, SpO_2 95% on ambient air, respiratory rate 16 per minute, and body temperature 37.2°C. Even after infusion of 1.5 litres of intravenous physiologic saline, her blood pressure remained around 100/80 mm Hg. Vasopressor drugs were not used. Abdominal examination showed tenderness in the right lower quadrant without signs of peritoneal irritation. The physical examination was otherwise normal.

INVESTIGATIONS

Laboratory tests revealed hyponatraemia, normal blood glucose levels and a normal eosinophil count. A chest and abdominal CT scan showed the same results as 2 weeks previously. With the findings of abdominal pain, infusion-resistant hypotension, hyponatraemia and a history of nivolumab administration, AI as an irAE caused by nivolumab was suspected. Ulcerative colitis as an irAE was considered less likely because bowel movements were normal, haematochezia was absent, and a CT scan did not show intestinal oedema. The patient was hospitalised for further evaluation without initiation of steroid therapy.

Early-morning sampling revealed low levels of serum ACTH (0.75 pmol/L) and serum cortisol (34.5 nmol/L). Brain MRI showed a normal pituitary gland. The rapid ACTH test provoked an increase in the cortisol level. In contrast, a corticotropin-releasing hormone stimulation test demonstrated no increase in the ACTH level or the cortisol level (figure 1A). A thyrotropin-releasing hormone stimulation test showed a low thyroid-stimulating hormone response, which was thought to be due to the use of levothyroxine and thiamazole (figure 1B). In Japan, combination therapy with levothyroxine and thiamazole is one treatment option for a patient with recurrent, unstable Graves' disease that is difficult to control when treated with thiamazole alone. Further stimulation tests showed no other pituitary hormone abnormalities (figure 1C,D). Based on these findings, we diagnosed IAD due to nivolumab.

TREATMENT

Nivolumab therapy was stopped, and on the seventh hospital day, daily administration of 15 mg of oral hydrocortisone was initiated. Oral administration was selected as her general condition was

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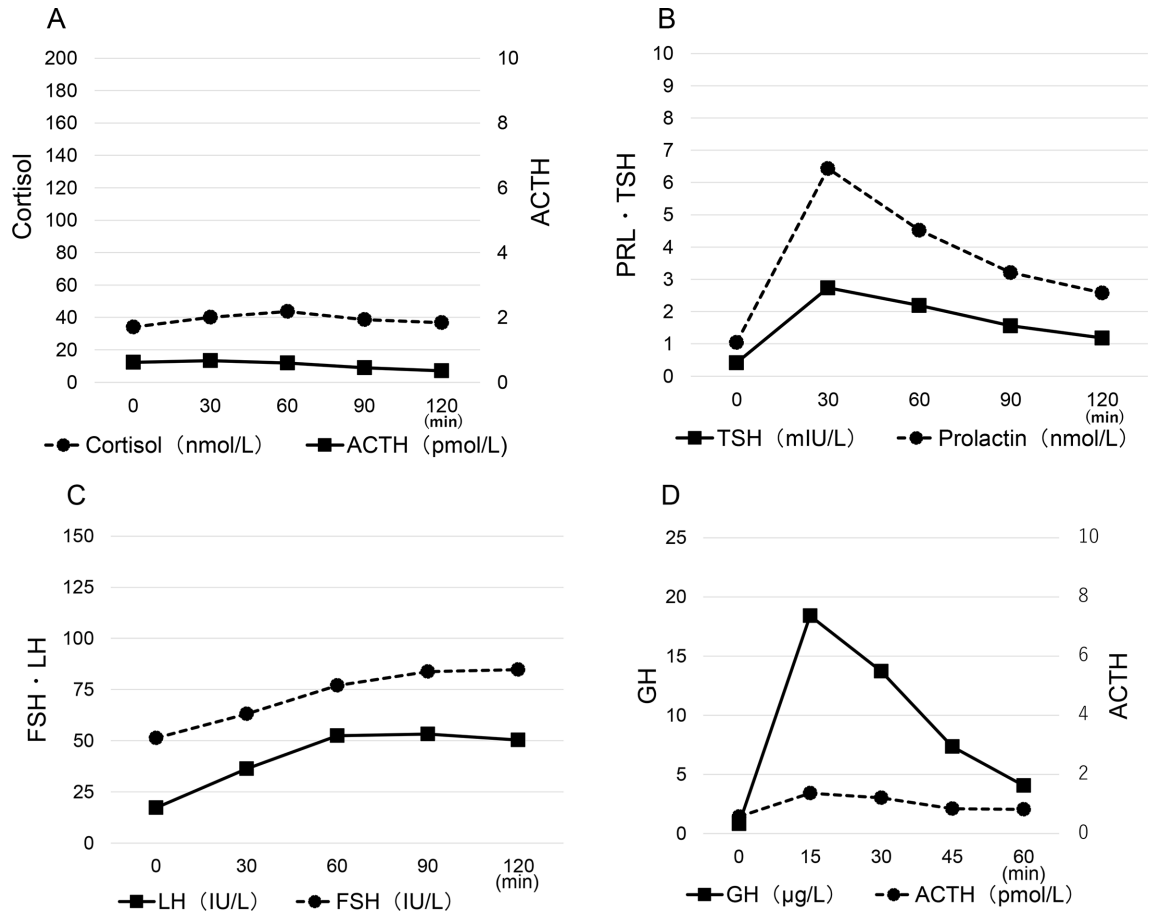

Figure 1 Stimulation tests. (A) Corticotropin-releasing hormone (CRH) stimulation test. (B) Thyrotropin-releasing hormone (TRH) stimulation test. (C) Gonadotropin-releasing hormone (GnRH) stimulation test. (D) Growth hormone-releasing peptide-2 (GHRP-2) test. CRH stimulation test demonstrated no increase in the ACTH level or the cortisol level. TRH stimulation test showed a low TSH response, which was thought to be due to the use of levothyroxine and thiama:zole. GnRH stimulation test and GHRP-2 stimulation test showed a normal response. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinising hormone; PRL, prolactin; TSH, thyroid-stimulating hormone.

stable although she still had mild abdominal pain with a blood pressure of about 100/80 mm Hg.

OUTCOME AND FOLLOW-UP

On the eighth hospital day, her abdominal pain, fatigue and hypotension started improving. On the 11th hospital day, all the symptoms had resolved and the patient was discharged on hydrocortisone 15 mg orally daily. She continued this dose during her outpatient follow-up. Some weeks later, her serum sodium levels returned to within normal limits.

DISCUSSION

We wish to emphasise two important clinical issues: first, nivolumab can cause IAD. Second, IAD can present with abdominal pain as an initial symptom, leading to delayed diagnosis. Like other ICIs, nivolumab can cause irAEs involving many organs, such as the gastrointestinal tract, endocrine glands, skin and liver.[4] Endocrine-related adverse events include thyroid dysfunction, hypophysitis, AI and diabetes mellitus. The mechanism underlying irAEs remains unknown. A systematic review and meta-analysis of ICIs reported that among nivolumab-treated patients (total number of patients: 3317), 2.0% experienced primary AI, and 0.5% experienced hypophysitis. The incidence of secondary AI is unclear.[2 4 9]

IAD is also rarely caused by ICIs. The precise incidence of IAD related to nivolumab is unknown, although there are some case reports. We show the characteristics of the 29 patients who exhibited IAD related to nivolumab in table 1. The male to female ratio is 21 to 8. About 90% of patients were between the ages of 50 and 80. Regarding the time to onset after the initiation of nivolumab treatment, 24 cases developed IAD after 5–33 courses of treatment, while five cases suffered from IAD even after discontinuation of nivolumab (figure 2). In 29 cases with nivolumab-related IAD (table 1), common manifestations include fatigue, anorexia and nausea/vomiting, while only the present case complained of abdominal pain (figure 3).

In addition, nivolumab is a target of all-case surveillance studies in the post-marketing setting as requested by the Pharmaceuticals and Medical Device Agency and Ministry of Health, Labour and Welfare in Japan. Results from this agency showed 251 cases of hypopituitarism or hypophysitis out of over 20 000 cases on nivolumab treatment from 4 July 2014 to 31 January 2021.[10] Although abdominal pain is a recognised symptom of AI and common especially in patients with antiphospholipid antibody syndrome, no case reports reported patients who had abdominal pain at the onset of nivolumab-related IAD.[11 12]

The diagnosis of IAD can be delayed because of its nonspecific presentation.[13 14] In the present case, the time from onset to diagnosis was thought to be 2 months. This is because the patient

Table 1 Review of case reports with nivolumab-related IAD

Case	Age sex	Primary disease	Time to onset		Initial symptoms	Ref.
			During treatment (courses)	After cessation (months)		
1	54/M	Lung cancer	8		Fatigue, anorexia, nausea, body pain	15
2	64/M	Lung cancer	7		Fatigue, anorexia, nausea, body pain	15
3	57/M	Lung cancer	6		Fatigue, anorexia, nausea, body pain	15
4	76/F	Melanoma	9		Fatigue, anorexia, nausea, body pain	15
5	70/M	Urothelial cancer	9		Fatigue, anorexia, nausea	16
6	50 s/M	Head and neck cancer	8		Fatigue, difficulty walking	17
7	69/M	Head and neck cancer	8		Fatigue, anorexia, nausea	18
8	73/M	Head and neck cancer	10		Fatigue, anorexia, arthralgia	18
9	69/F	Lung cancer		4	Fatigue, anorexia	19
10	52/F	Breast cancer		1	Fatigue	20
11	72/F	Melanoma		4	Fatigue, anorexia	21
12	79/M	Melanoma	20		Anorexia, nausea, difficulty walking	22
13	71/M	Renal cancer	14		Fatigue, anorexia, impaired consciousness	23
14	66/M	Renal cancer	8		Anorexia, exertional dyspnoea	24
15	73/M	Lung cancer		7	Fatigue, anorexia, weight loss	25
16	58/M	Melanoma		1	Fatigue, impaired consciousness	26
17	53/M	Melanoma	7		Fatigue, vomiting, myalgia	27
18	72/M	Melanoma	14		Fatigue, anorexia, vomiting	27
19	63/F	Lung cancer	17		Fatigue, anorexia, myalgia, difficulty walking	28
20	54/M	Renal cancer	12		Fatigue	29
21	74/F	Renal cancer	5		Fatigue, anorexia, nausea	30
22	75/M	Lung cancer	12		Fatigue, anorexia	31
23	60/M	Lung cancer	11		Fatigue, anorexia, exertional dyspnoea	32
24	72/M	Lung cancer	10		Fatigue, anorexia, vomiting	32
25	71/M	Lung cancer	10		Fatigue, anorexia, nausea	32
26	39/M	Melanoma	13		Fatigue, dizziness	33
27	55/M	Lung cancer	33		Fatigue, asthenia, depression, weight loss	34
28	76/F	Melanoma	9		Fatigue, anorexia, bradykinesia	35
29	81/F	Mesothelioma	8		Fatigue, abdominal pain	Present case

IAD, isolated adrenocorticotropic hormone deficiency.

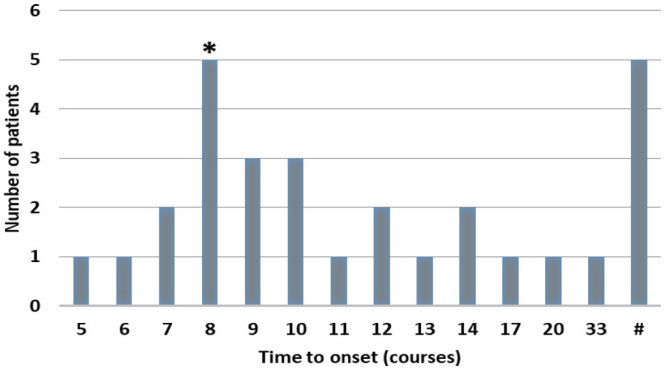

Figure 2 Time to onset. Time to onset of isolated adrenocorticotropic hormone deficiency (IAD) from the initiation of nivolumab therapy in 29 patients with nivolumab-related IAD. Twenty-four cases developed IAD after 5 to 33 courses of treatment, while five cases suffered from IAD even after discontinuation of nivolumab. *Marks our case. #Signifies onset after discontinuation of nivolumab therapy. Two cases developed IAD 1 month after the discontinuation, two cases after 4 months, and one case after 7 months.

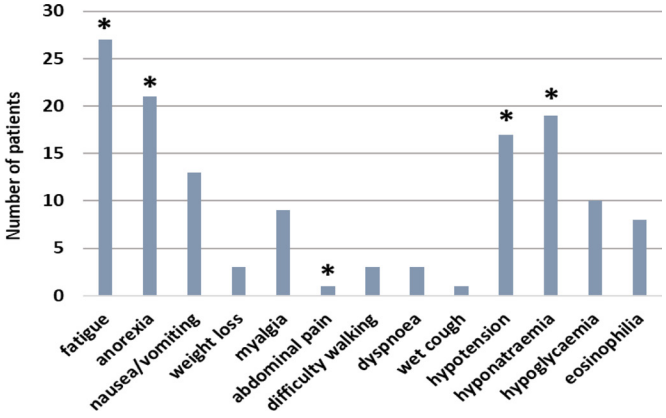

Figure 3 Clinical manifestations. Clinical manifestations in 29 patients with nivolumab-related IAD. Common manifestations include fatigue, anorexia and nausea/vomiting, while only the present case complained of abdominal pain. *Denotes the symptoms present in our case. IAD, isolated adrenocorticotropic hormone deficiency.

Patient's perspective

I started to feel mild lower abdominal pain at times a few days after the colon surgery. I thought it was related to the surgery and that it would get better with time. However, it continued mildly off and on after discharge. The pain had nothing to do with meals and nothing made it better nor worse. I complained of the pain when I saw my surgery doctor for a follow-up 2 months after the surgery. He did a physical examination and took an abdominal CT scan, which did not show any abnormality. He told me to see how it would go with painkillers taken as needed. I got confused, wondering what caused the pain and why the cause was not revealed. Two weeks later, I went to the emergency room because the pain got worse and was hospitalised.

The doctors in charge explained to me that nivolumab caused the pain, though I did not realise it. My abdominal pain got better a few days after steroid treatment. Although my doctors explained how the anti-cancer drug caused the abdominal pain, it was a bit difficult for me to fully understand. However, I felt relieved because the pain got better and the cause was revealed.

Learning points

- Nivolumab can cause isolated adrenocorticotropic hormone deficiency (IAD) as an immune-related adverse events.
- IAD can cause abdominal pain, which can lead to delayed diagnosis because of its poor specificity.
- We should consider adrenal insufficiency (AI) as a possible diagnosis when a patient on nivolumab has abdominal pain and has no explanatory findings in imaging tests. Infusion-resistant hypotension and hyponatraemia might further suggest AI.

developed abdominal pain just after abdominal surgery, which masked the correct diagnosis. We suspected AI not only because she had no other organic abnormality causing abdominal pain but also because she presented with infusion-resistant hypotension and hyponatraemia. A previous case report emphasised that hyponatraemia can be a predictor of IAD associated with nivolumab.[15]

Contributors KH conceived the case report, reviewed the literature and prepared the first manuscript. CS and KH were in charge of taking care of the patient. MT reviewed the first manuscript and cooperated with KH to complete the final draft. YN supervised the whole process. All the authors approved the final manuscript and this submission.

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ORCID iD
Koichi Hata http://orcid.org/0000-0001-5705-3793

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