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【 CASE REPORT 】

Rheumatoid Arthritis Symptoms Diagnosed by Rheumatic Immune-related Adverse Events Caused by Nivolumab in a Patient with Esophageal Cancer

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Abstract:
This report described the case of a 70-year-old man who developed polyarthralgia after nivolumab treatment for recurrent esophageal cancer. Arthritis developed after initiating nivolumab therapy, and the patient tested positive for rheumatoid factor and anti-citrullinated peptide antibodies. The hand and elbow joints were already deformed, suggesting that he had had rheumatoid arthritis for several years and that the symptoms had only become apparent after nivolumab administration. This patient had rheumatoid arthritis, which was diagnosed as a nivolumab-induced rheumatic immune-related adverse event (rh-irAEs). Arthralgia during nivolumab administration can occur in rh-irAE cases. Patients should be assessed for autoimmune diseases before initiating immune checkpoint inhibitors.

Key words: esophageal cancer, rheumatoid arthritis, nivolumab, rheumatic immune-related adverse events, talaporfin sodium photodynamic therapy

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Introduction

Nivolumab is an anti-programmed cell death-1 (PD-1) monoclonal antibody and is currently used as an immune checkpoint inhibitor (ICI) in many types of carcinoma. It was approved in Japan in 2020 for the treatment of advanced or recurrent esophageal cancer that cannot be treated with curative resection. A variety of immune-related adverse events (irAEs) occur with ICIs (1, 2), affecting almost all organs. There are also reports of rheumatic irAEs (rh-irAEs); however, they have not been fully studied, and their characteristics remain unknown (3).

We herein report a case of rheumatoid arthritis diagnosed after nivolumab was administered for esophageal cancer.

Case Report

We encountered a 70-year-old man treated with chemoradiation therapy (10 courses of full dose with 5-fluorouracil and cisplatin therapy+radiotherapy 50.4 Gy/28 times) for upper thoracic esophageal cancer (cT4bN2M0 stage IVa) (Fig. 1). The patient was in complete remission following chemoradiation therapy, but one year later, he underwent photodynamic therapy (PDT) for ectopic local recurrence of esophageal cancer. The patient had another ectopic local recurrence one year later and underwent PDT twice in total (Fig. 2A, B). Interstitial pneumonia was noted during chemoradiation therapy. However, the patient's pneumonia did not worsen during the treatment, and no treatment was administered. After approximately two years of follow-up without treatment (after PDT) for esophageal cancer, positron emission tomography-computed tomography (PET-CT) revealed newly enlarged lymph nodes around the gastric cardia and fluorine-18-deoxyglucose accumulation, and ultrasound endoscopic puncture aspiration was performed (Fig. 2C-E). The patient was diagnosed with esophageal cancer lymph node metastasis and admitted for nivolumab

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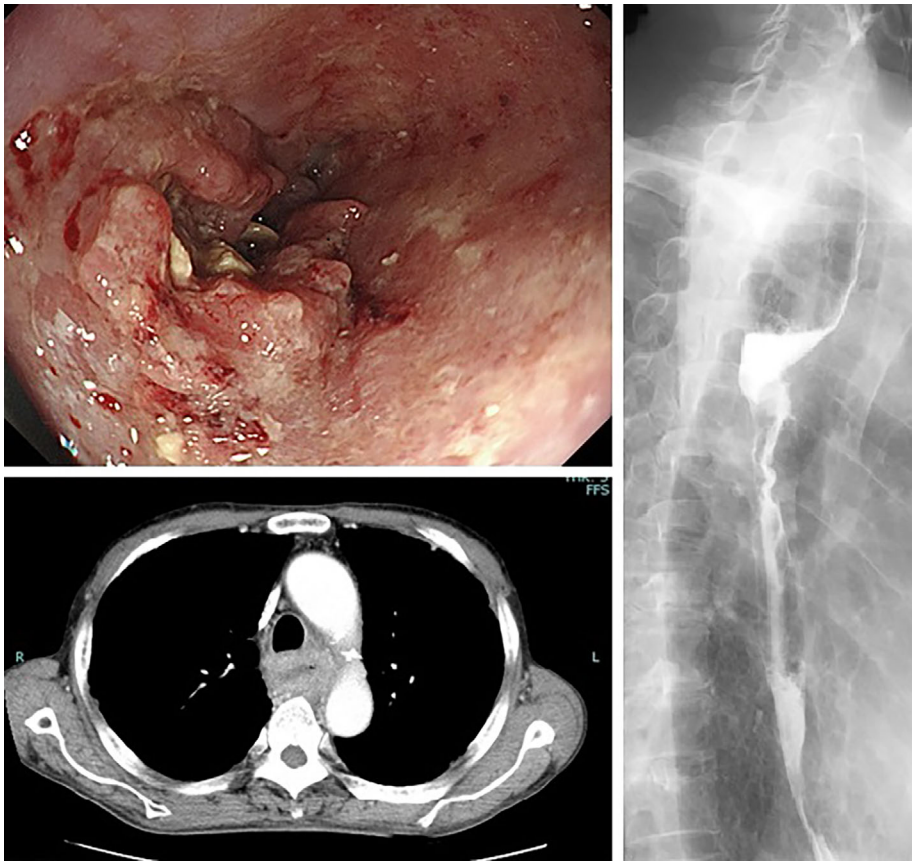

Figure 1. Endoscopic, computed tomography, and esophagography findings showing esophageal cancer in the upper thoracic esophagus before treatment at the time of the initial diagnosis.

induction.

He developed a fever (38°C) on the night of nivolumab administration. Suspecting a bacterial infection, blood cultures were obtained, and antimicrobial administration was initiated. Blood cultures were negative, and the cause of the fever was unclear. Although it could have been an infusion reaction caused by the administration of nivolumab, generalized arthralgia [Common Terminology Criteria for Adverse Events (CTCAE) grade 3] appeared on the seventh day of administration, and the symptoms did not improve despite oral loxoprofen. On the 12th day after administration, the patient was examined by a rheumatologist for multiple joint pain. The patient had the following vital signs: body temperature, 37.2°C; pulse, 83 beats/min; blood pressure, 99/68 mmHg; oxygen saturation, 95% (room air); and respiratory rate, 16 breaths/min. Fine crackles were heard bilaterally in the respiratory sounds, and no edema or skin rash was observed in the lower legs. He had polyarthritis mainly in the knee and elbow joints and the following biochemical findings: C-reactive protein, 10.23 mg/dL; rheumatoid factor (RF), 152.8 IU/mL; anti-citrullinated peptide (CCP), 447 U/mL; matrix metalloproteinase-3, 2,204 ng/mL; and erythrocyte sedimentation rate, 135 mm/h.

X-ray of the hand showed carpal bone erosions, metacarpophalangeal (MCP) joint subluxation and proximal interphalangeal (PIP) joint space narrowing, and X-ray of the elbow showed joint space narrowing and multiple erosions (Fig. 3). Chest CT revealed interstitial pneumonia just below the pleura and predominantly at the base of the lung, but there were no significant changes compared to the previous examination. The hand and elbow joints were already deformed, suggesting that the patient had been experiencing rheumatoid arthritis for at least several years. An orthopedic examination was negative for pyogenic arthritis or pseudogout.

Rheumatoid arthritis, which was undiagnosed because of mild spontaneous joint pain, manifested with the administration of nivolumab. On the 17th day of nivolumab administration, 500 mg/day of salazosulfapyridine and 5 mg/day of prednisolone (PSL) were started. Salazosulfapyridine was prescribed as the patient had both interstitial pneumonia and renal dysfunction. Furthermore, a small dose (5 mg) of PSL was also prescribed as a result of his joint pain decreasing with loxoprofen and because due to interstitial pneumonia, a high dose of steroids could be fatal if a respiratory infection were to be induced.

After 2 weeks of treatment, the dose of salazosulfapyridine was increased to 1,000 mg/day as no side effects were observed. Following the dose increase, no side effects were noted, joint swelling and the fever decreased, and tenderness and spontaneous pain improved. As the patient's symptoms had stabilized, no increase in drug dosage or addition of new drugs was performed. The dose of PSL was also not reduced in order to avoid the possibility of pain aggravation.

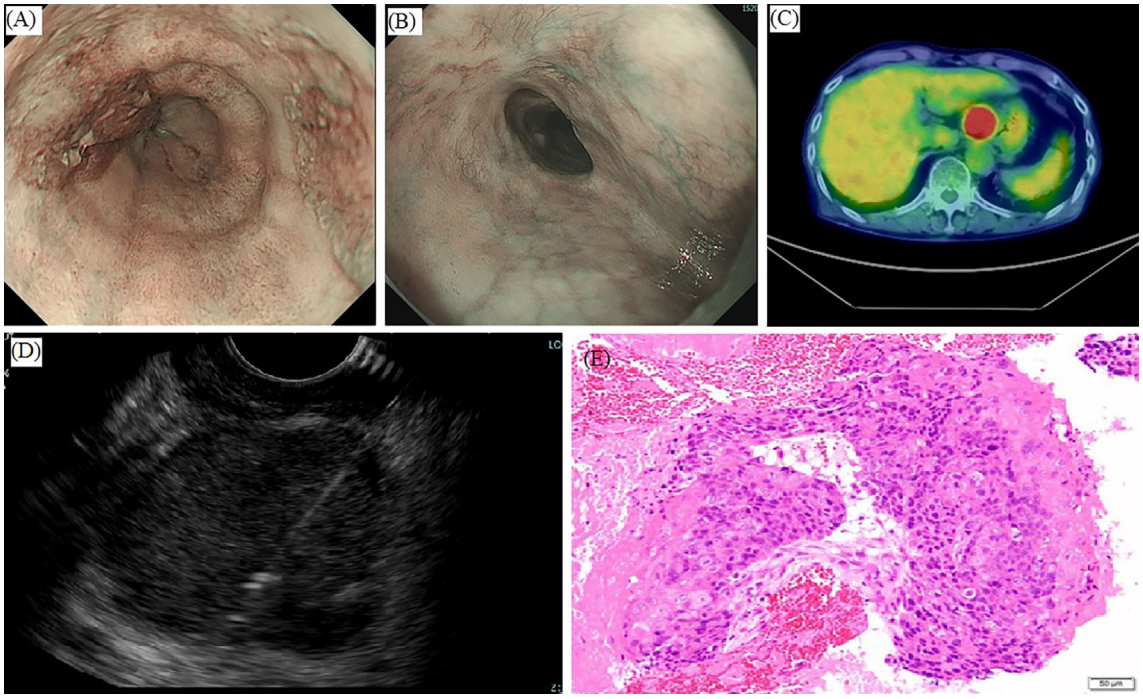

Figure 2. **(A) Endoscopic findings with narrow-band imaging showing esophageal cancer with local recurrence after chemoradiation therapy. (B) Endoscopic findings with narrow-band imaging showing local complete remission of esophageal cancer after photodynamic therapy. (C) PET-CT revealing enlarged lymph nodes around the gastric cardia and the accumulation of fluorine-18-deoxyglucose. (D) Ultrasound image showing ultrasound endoscopic puncture aspiration of the lymph nodes around the gastric cardia. (E) Histopathology of the lymph nodes around the gastric cardia revealing squamous cell carcinoma. Bar=50μm. PET-CT: positron emission tomography-computed tomography**

Chemotherapy was discontinued due to the onset of symptoms of rheumatoid arthritis, but it was resumed after the regimen was changed to weekly paclitaxel. CT after one course of weekly paclitaxel administration showed mild shrinkage of lymph nodes around the gastric cardia, and treatment was judged to be a partial response (PR) and continued.

Discussion

We encountered a case of rheumatoid arthritis caused by nivolumab administration for esophageal cancer. In recent years, the mechanism underlying immune tolerance in cancer cells has been elucidated, the development of cancer immunotherapy has been remarkable, and the clinical tumor effects of ICIs have been demonstrated (4). In Japan, nivolumab, an anti-PD-1 antibody, was approved for metastatic malignant melanoma in 2014. ICIs have the potential to cause irAEs owing to their mechanism of action (5). rh-irAEs have also been reported but have not yet been fully studied or characterized. rh-irAEs include rheumatoid-like symptoms and rheumatic diseases, such as arthralgia, myalgia, arthritis, and tendinitis. However, symptoms of arthralgia and myalgia account for the majority of reports, and reports of the development of RF and anti-CCP-positive rheumatoid arthritis, as in this case, are rare (6-8). Patients with pre-existing autoimmune diseases (ADs) are largely excluded from clinical trials of ICIs (9, 10). Therefore, data on the safety of ICIs in patients with pre-existing AD are relatively limited. However, patients with rheumatic AD are five times more likely to have an AD flare than patients with non-rheumatic AD (7).

The present patient received talaporfin sodium PDT (TS-PDT) for local recurrence after chemoradiotherapy (CRT) for esophageal cancer and achieved complete local remission. TS-PDT for local failure after CRT in patients with esophageal squamous cell carcinoma has recently been reported to be highly effective and less invasive than other treatment methods (11, 12). However, our patient experienced lymph node metastasis approximately two years later, and nivolumab was administered. A fever was observed on the day of nivolumab administration, and generalized arthralgia appeared during a detailed examination of the fever source. Rheumatoid arthritis was diagnosed based on markedly high levels of RF and anti-CCP and the presence of bone erosion on X-ray of the hand and elbow joints.

It was hypothesized that the symptoms of mild and undiagnosed rheumatoid arthritis had manifested as irAEs caused by nivolumab. Although new rh-irAEs occurred sometime after the start of ICI administration [median, 38 (range, 8-137) weeks], rh-irAEs in patients with pre-existing rheumatic diseases have been reported to flare up relatively quickly [median, 4.6 (range, 1-43) weeks] after ICI administration (13). Patients with new rh-irAEs have also been re-

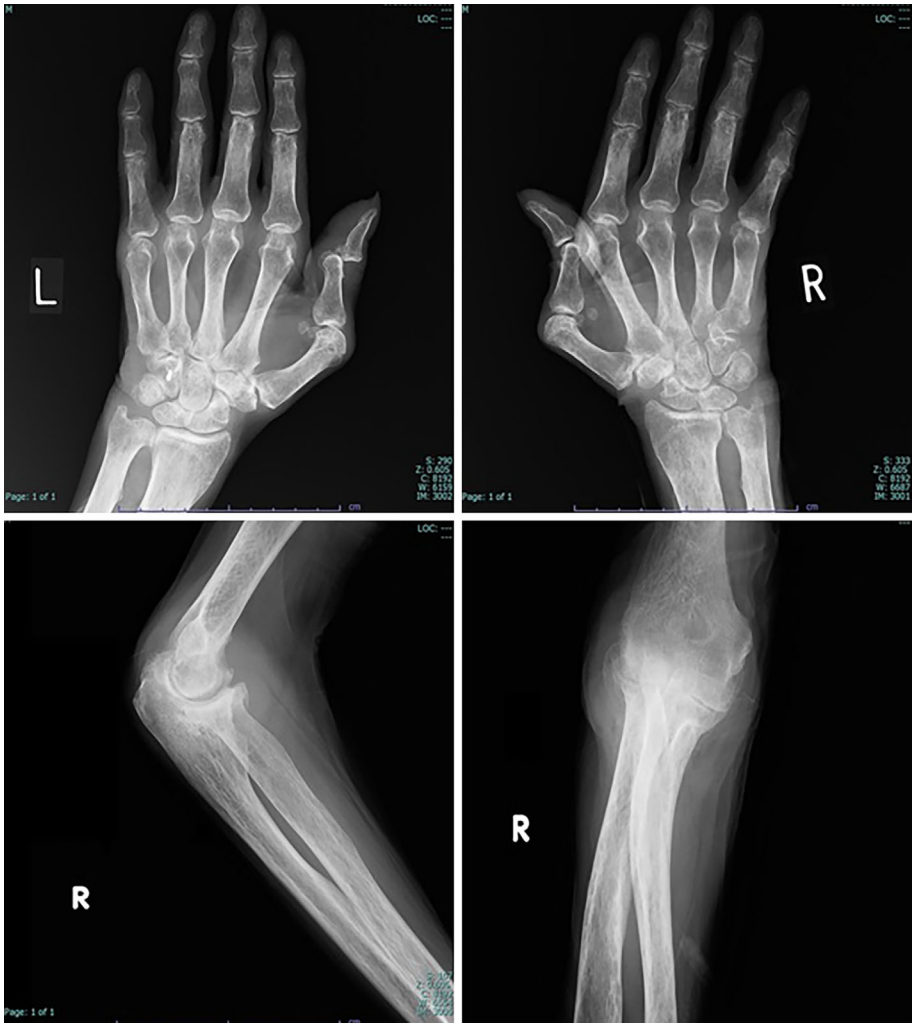

Figure 3. **X-ray of the hand showing carpal bone erosion, metacarpophalangeal (MCP) joint subluxation and proximal interphalangeal (PIP) joint space narrowing. X-ray of the elbow showing joint space narrowing and multiple erosions.**

ported to have less morning stiffness, less bone erosive changes, and lower hemoglobin levels and lymphocyte counts than patients with pre-existing rheumatic diseases (14). Therefore, we concluded that our patient had already developed rheumatoid arthritis prior to ICI administration. In addition, there is a difference in symptoms before the onset of arthritis between anti-CCP-positive and anti-CCP-negative patients with rheumatoid arthritis, and patients with anti-CCP-positive arthritis have a faster progression of arthritis after the onset of arthritis than anti-CCP-negative patients (15). Therefore, the onset of arthritis may have been early in this case as well.

Belkhir et al. reported six cases of new-onset rheumatoid arthritis during anti-PD-1 treatment in patients with no history of rheumatoid arthritis or arthritis, three of whom underwent anti-CCP testing before anti-PD-1 treatment. Two patients were positive for anti-CCP, suggesting that anti-PD-1 may trigger the development of rheumatoid arthritis in patients who are in a prodromal state of rheumatoid arthritis and have not yet developed joint symptoms (6). PD-1 accounts for a large proportion of musculoskeletal irAEs among ICIs (16), and in this case, RF was high in blood tests before the start of chemotherapy. Therefore, it was necessary to check anti-CCP levels and consult a rheumatologist prior to administration.

Early detection of rheumatoid arthritis is important because prolonged arthritis can lead to serious functional impairment of the destroyed joints and a significant decrease in the quality of life. In the present case, the worsening of arthralgia made it difficult to continue chemotherapy, and it took time to introduce new chemotherapy. Guidelines for the treatment of rheumatoid arthritis recommend the use of disease-modifying anti-rheumatic drugs (DMARDs) for rheumatoid arthritis (17). In April 2020, the European League Against Rheumatism recommendations for the diagnosis and treatment of rh-irAEs were reported by Kostine et al. (18). Three treatment modality escalations were proposed: (a) local/systemic glucocorticoids if symptoms do not improve with symptomatic treatment, tapered to the lowest efficient dose; (b) conventional synthetic DMARDs if the response to glucocorticoids is inadequate or for steroid preservation; and (c) synthetic DMARDs for severe or refractory

Table. Laboratory Data on Admission.

<Complete blood count>			<Blood chemistry>		
	Unit	Normal range		Unit	Normal range
WBC	7,700 /μL	3,300-8,800	TP	7.5 g/dL	6.6-8.1
Neutrophil	68 %	36-70	Alb	3.1 g/dL	4.1-5.1
Lymphocyte	20 %	22-53	Total-Bil	0.5 mg/dL	0.4-1.5
Eosinophil	6 %	0-8	AST	17 U/L	13-30
Monocyte	5 %	4-12	ALT	11 U/L	10-42
Basophil	1 %	0-1	ALP	318 U/L	38-113
RBC	351 /10^4μL	440-570	γ-GT	20 U/L	13-64
Hb	11.2 g/dL	12-17	LD	320 U/L	124-222
Plt	21.1 /10^4μL	12.5-34.3	CK	39 U/L	59-248
			Na	137 mEq/L	138-145
<Coagulation>			K	4.2 mEq/L	3.6-4.8
PT-INR	1.11	0.87-1.20	Cl	101 mEq/L	101-108
APTT	28 s	23.3-38.2	BUN	28.2 mg/dL	8-20
D-dimer	15.7 μg/mL	<1.0	Cr	1.72 mg/dL	0.65-1.07
			eGFR	31 mL/min/1.73m^2	
			CRP	1.94 mg/dL	<0.15
			HbA1c	5.2 %	4.9-6.0
			KL-6	479 U/mL	<500
			SP-D	155 ng/mL	<110
			TSH	2.55 μU/mL	0.27-4.2
			FT4	1.09 ng/dL	0.93-1.7
			ANA		
			Homogeneous	160	<40
			Speckled	160	<40
			RF	204 U/mL	<15
			CEA	2.8 ng/mL	<5.0
			SCC	2.6 ng/mL	<1.5

Alb: albumin, ALP: alkaline phosphatase, ALT: alanine transaminase, ANA: antinuclear antibody, APTT: activated partial thromboplastin time, AST: aspartate transaminase, Bil: bilirubin, BUN: blood urea nitrogen, CEA: carcinoembryonic antigen, CK: creatine kinase, Cl: chloride, Cr: creatinine, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, FT4: free thyroxine, γ-GT: γ-glutamyl transpeptidase, Hb: hemoglobin, HbA1c: hemoglobin A1c, K: potassium, KL-6: sialylated carbohydrate antigen KL-6, LDH: lactate dehydrogenase, Na: sodium, Plt: platelets, PT-INR: prothrombin time-international normalized ratio, RBC: red blood cells, RF: rheumatoid factor, SCC: squamous cell carcinoma antigen, SP-D: serum surfactant protein-D, TP: total protein, TSH: thyroid-stimulating hormone, WBC: white blood cells

irAEs. Biological DMARDs should be administered to treat severe or refractory irAEs. Considering the presence of preexisting interstitial pneumonia and renal dysfunction, salazosulfapyridine and PSL were administered in the present case. Corticosteroid treatment is often used for immunological adverse events associated with nivolumab and has been reported to not affect the therapeutic effect of nivolumab (19, 20). The response to treatment was good, with a resultant improvement in the symptoms. However, nivolumab treatment was not restarted because of residual synovitis. There are reports that anti-PD-1 therapy can be continued in many patients (6, 8), suggesting that nivolumab can also be continued in patients with rheumatoid arthritis with pain and disease control. Furthermore, patients with rh-irAEs have a significantly higher tumor response rate than those without rh-irAEs (20), which should be considered. Treatment of rh-irAEs requires close cooperation between the treating oncologist and rheumatologist. Therefore, it is necessary to determine the optimal treatment for each patient according to the CTCAE grade.

Conclusion

We reported a case of rheumatoid arthritis diagnosed after nivolumab administration for esophageal cancer. Arthralgia during nivolumab treatment requires early intervention for rh-irAEs. In addition, close cooperation between oncologists and rheumatologists in charge of treatment is necessary to determine the optimal treatment for each patient according to the CTCAE grade.

The authors state that they have no Conflict of Interest (COI).

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