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【 CASE REPORT 】

Synchronous Occurrence of Bazex Syndrome and Remitting Seronegative Symmetrical Synovitis with Pitting Edema Syndrome in a Patient with Lung Cancer

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Abstract:
A 69-year-old man developed bilateral polyarthritis, edematous extremities, and skin desquamation on the fingers and ears. He did not meet the criteria for any connective tissue disease, including rheumatoid arthritis. An examination revealed advanced lung cancer. His systemic manifestations were attributed to paraneoplastic Bazex syndrome and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome. Treatment with pembrolizumab (an anti-programmed death-1 antibody) for lung cancer relieved his symptoms and shrank the lung tumor. Bazex and RS3PE syndromes are rare paraneoplastic diseases. We herein report this unique case of synchronous development of these two paraneoplastic syndromes in the presence of advanced lung cancer.

Key words: Bazex syndrome, lung cancer, paraneoplastic syndrome, RS3PE syndrome

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Introduction

Bazex syndrome is a rare paraneoplastic syndrome characterized by bilateral, symmetrical keratotic eruptions on the distal extremities, nose, and pinna (1). Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome is characterized by symmetrical arthritis accompanying pitting edema in the absence of rheumatoid factor. It sometimes occurs as a paraneoplastic syndrome (2).

We herein report a unique case of simultaneously occurring Bazex and RS3PE syndromes in a patient with lung cancer.

Case Report

A 69-year-old man presented at our hospital with a 6-month history of gradually worsening edema of the fingers and legs, skin eruptions on the fingers and ears, and deformities of the finger joints. He also had a history of type 2 diabetes mellitus and was a 50-pack-year smoker. He exhibited pitting edema of the fingers and legs, desquamating eruptions on the extensor side of the fingers and ears, and deformities of the distal interphalangeal (DIP), proximal interphalangeal, and meta-phalangeal joints. He could not straighten his fingers (Fig. 1A-C). Blood tests showed a slight elevation in erythrocyte sedimentation rate of 12 mm/h and a marked elevation in vascular endothelial growth factor (VEGF) of 541 pg/mL (an upper limit of 38.3 pg/mL). There were no specific autoantibodies associated with connective tissue diseases, including rheumatoid factor (Table). The patient's thyroid, renal, and cardiac functions were normal (ejection fraction on an echocardiogram was 56.8%). Plain radiography showed the finger joint deformities without accompanying bone erosion (Fig. 1D). A biopsy of a finger eruption revealed cornification, dermal fibrosis, and

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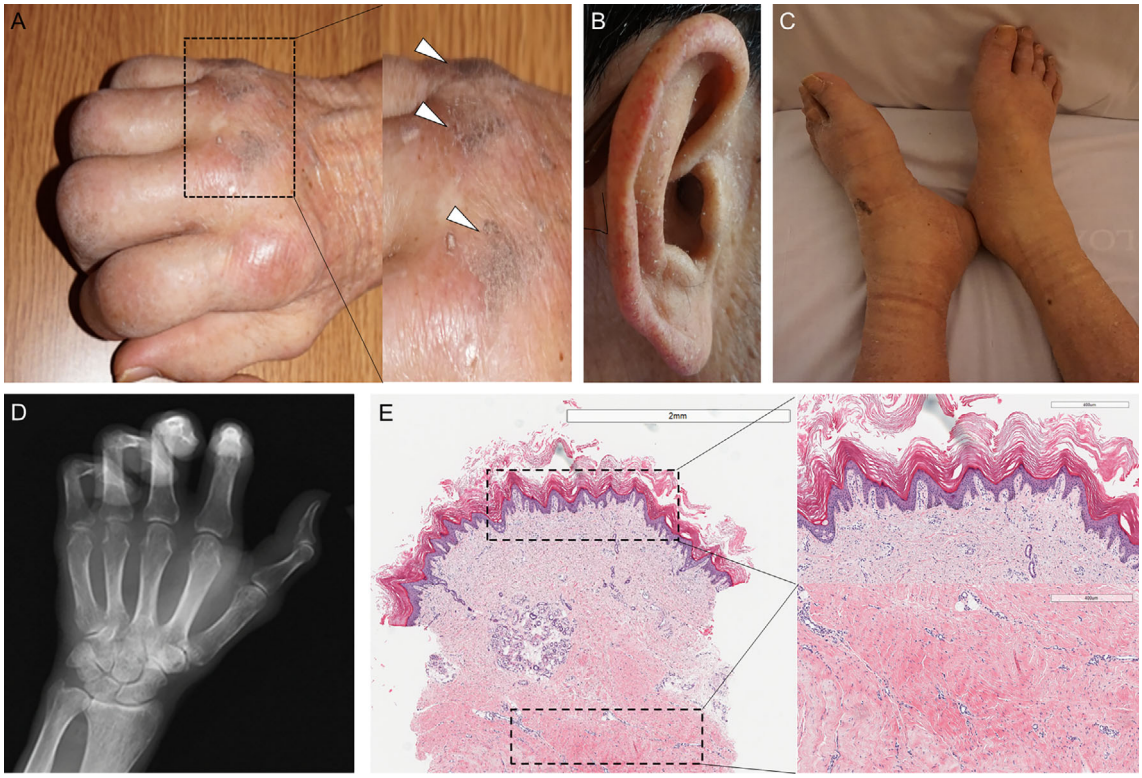

Figure 1. **(A) Desquamating eruptions were apparent on the extensor sides of the fingers (arrowheads). Also present were edema and deformities of the distal interphalangeal, proximal interphalangeal, and meta-phalangeal finger joints. In addition, the fingers could not be straightened. (B) Desquamating eruptions on the ears. (C) Pitting edema of the lower legs. (D) Radiography showed deformities of the finger joints without bone erosion. (E) A skin biopsy of a finger eruption showed cornification (upper right), dermal fibrosis, and hyperplasia of subcutaneous collagen fibers (lower right).**

hyperplasia of subcutaneous collagen fibers (Fig. 1E). Chest computed tomography (CT) revealed a mass (maximum diameter of 73 mm) in the lung right upper lobe and mediastinal lymphadenopathy (Fig. 2A). Positron emission tomography CT showed the uptake of ^{18}F-fluorodeoxyglucose (FDG) in the bilateral shoulder, hip, and knee joints in addition to the cancerous lung tumor and mediastinal lymphadenopathy (Fig. 2B). There was only a mild ^{18}F-FDG uptake in the finger joints. Whole-body CT demonstrated no bone destruction or regeneration in the joints with the increased ^{18}F-FDG uptake, which was suggestive of multiple arthritis, but not bone metastases. Magnetic resonance imaging revealed brain metastases (Fig. 2C). A transbronchial biopsy of the lung tumor showed adenocarcinoma (Fig. 3A), which was diagnosed as stage IVB lung cancer. His skin eruptions and bilateral arthritis with pitting edema were attributed to the paraneoplastic Bazex and RS3PE syndromes, respectively.

The lung tumor expressed high levels of programmed death-ligand 1 (tumor proportion score >90%) without mutation of the epidermal growth factor receptor gene or the anaplastic lymphoma kinase fusion gene (Fig. 3B). Pembrolizumab (200 mg in a 21-day cycle), an anti-programmed death-1 antibody, was administered as the first-line therapy to decrease the size of the lung tumor (Fig. 4). Along with the shrunken lung cancer, the patient's leg edema, swelling of the finger joints, and skin eruptions were gradually relieved. Unfortunately, the deformities of the finger joints showed only mild improvement (Fig. 4). Pembrolizumab was discontinued after seven cycles at the request of the patient. After discontinuing this treatment, the deformities and swelling of the finger joints gradually deteriorated, and regrowth of the tumor occurred. The pitting edema of the legs and skin eruptions remained the same. He ultimately died of lung cancer 14 months after discontinuing pembrolizumab.

Discussion

The symmetrical polyarthritis with skin rash in the reported patient was suggestive of a connective tissue disease. However, a further examination revealed synchronous Bazex and RS3PE syndromes as well as advanced lung cancer. Along with the tumors responding to pembrolizumab, the symptoms associated with Bazex and RS3PE syndromes were somewhat alleviated. Although these two syndromes are rare paraneoplastic diseases, they can help diagnose cancers and influence the course of treatment. The early, accurate diagnosis of paraneoplastic syndromes is important in cancer therapy.

Table. **Laboratory Data.**

WBCs	6.32×10^3 /μL	IgG	1,566 mg/dL
RBCs	474×10^4 /μL	IgA	400 mg/dL
Hb	13.7 g/dL	IgM	100 mg/dL
Hct	42.4 %	CEA	56.6 ng/mL
Plt	20.2×10^4 /μL	SLX	85 U/mL
TP	6.9 g/dL	ANA	×40
Alb	3.5 g/dL	Speckled pattern	×40
T.bil	0.4 mg/dL	Cytoplasmic pattern	×40
AST	19 IU/L	RF	5.1 IU/L
ALT	10 IU/L	MMP-3	57.5 ng/mL
LDH	207 IU/L	CCP	0.6 U/mL
ALP	10 IU/L	Jo-1	Negative
γ-GT	25 IU/L	MDA-5	Negative
CK	60 IU/L	TIF1-γ	Negative
BUN	13.1 mg/dL	FT3	1.9 pg/mL
Cr	0.41 mg/dL	FT4	1.1 ng/dL
CRP	0.1 mg/dL	TSH	3.21 μU/mL
ESR	12 mm/h	NT-proBNP	264 pg/mL
ESR	28 mm/2h	VEGF	541 pg/mL

WBCs: white blood cells, RBCs: red blood cells, Hb: hemoglobin, Hct: hematocrit, Plt: platelets, TP: total protein, Alb: albumin, T.bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GT: γ-glutamyltranspeptidase, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IgG: immunoglobulin G, IgA: Immunoglobulin A, IgM: Immunoglobulin M, CEA: carcinoembryonic antigen, SLX: sialyl Lewis antigen, ANA: antinuclear antibody, RF: rheumatoid factor, MMP-3: matrix metalloproteinase-3, CCP: anti-cyclic citrullinated peptide antibody, Jo-1: anti-Jo1 antibody, MDA-5: melanoma differentiation-associated gene 5 antibody, TIF1-γ: transcriptional intermediary factor 1-gamma antibody, FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid-stimulating hormone, NT-proBNP: N-terminal pro-brain natriuretic peptide, VEGF: vascular endothelial growth factor

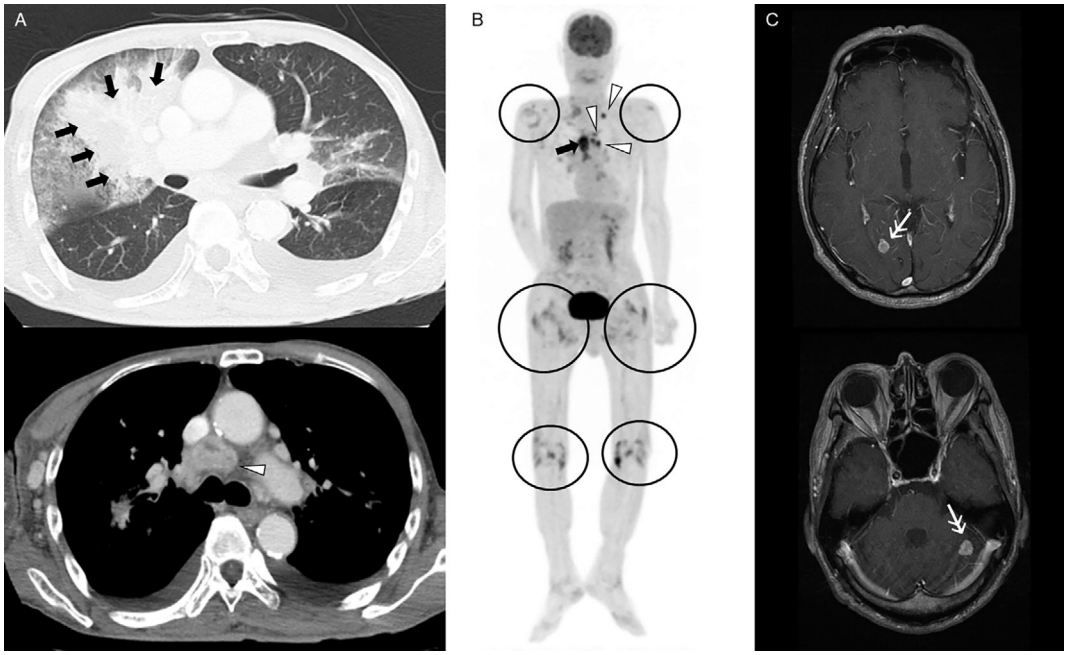

Figure 2. **(A) Computed tomography showed a mass (shadow) in the right upper pulmonary lobe (arrows) and mediastinal lymphadenopathy (arrowheads). (B) Positron emission tomography showed the uptake of ^{18}F-fluorodeoxyglucose in the bilateral shoulders, hips, and knee joints (circles). In addition to the pulmonary shadow (arrow), mediastinal lymphadenopathy was present (arrowheads). (C) Magnetic resonance imaging showed brain metastases (two-headed arrows).**

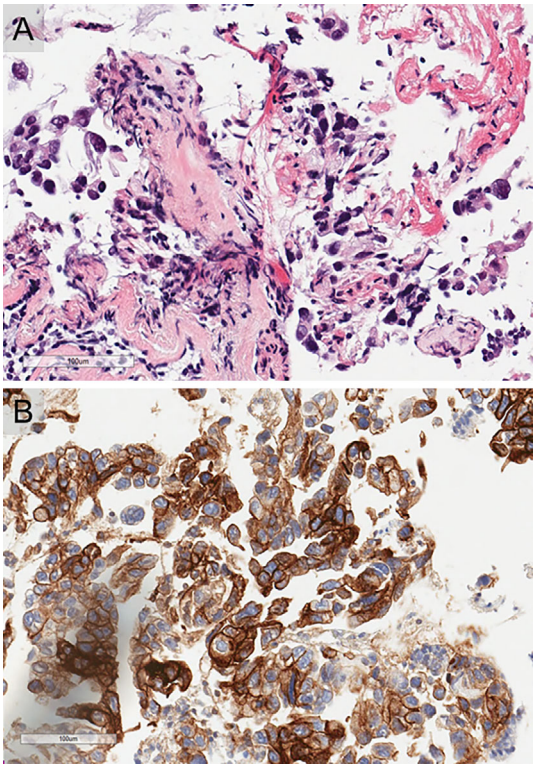

Figure 3. **(A) A transbronchial biopsy of the lung shadow revealed adenocarcinoma (Hematoxylin and Eosin staining). (B) The tumor showed high expression of programmed death-ligand 1 (PD-L1) (22C3 anti PD-L1 antibody, with a tumor proportion score of >90%).**

Paraneoplastic dermatoses, defined as skin manifestations of an internal malignancy, are sometimes observed in cancer patients. Specific features and associations with particular cancers have been reported for each paraneoplastic dermatosis (3). For Bazex syndrome, squamous cell carcinoma of the head and neck is the most common type of associated cancer, with lung cancer the second-most common (4). Among 77 patients with Bazex syndrome, 13 (16%) were also diagnosed with lung cancer (8 squamous cell carcinomas, 3 adenocarcinomas, 2 small cell carcinomas) (5). Although some of the paraneoplastic dermatoses occur sporadically, without the presence of a cancer, Bazex syndrome is strongly associated with a cancer presence and its clinical course (5). Therefore, when Bazex syndrome develops, the occurrence and/or relapse of cancer should be suspected.

It has been reported that 10-40% of RS3PE syndrome occurrences are associated with a malignant tumor (6, 7). Hematological, prostatic, and gastrointestinal cancers are most commonly associated, whereas lung cancer is uncommon (8). In the current case, the existence of bilateral polyarthritis with pitting edema, in the absence of rheumatoid factors, was consistent with the definition of RS3PE syndrome. The marked elevation in serum VEGF was also suggestive of RS3PE syndrome (9). However, there were some unusual clinical characteristics of RS3PE syndrome in the current case. First, the patient had no increased levels of C-reactive protein (CRP) or matrix metalloproteinase-3 (MMP-3), although several reports have described cases of

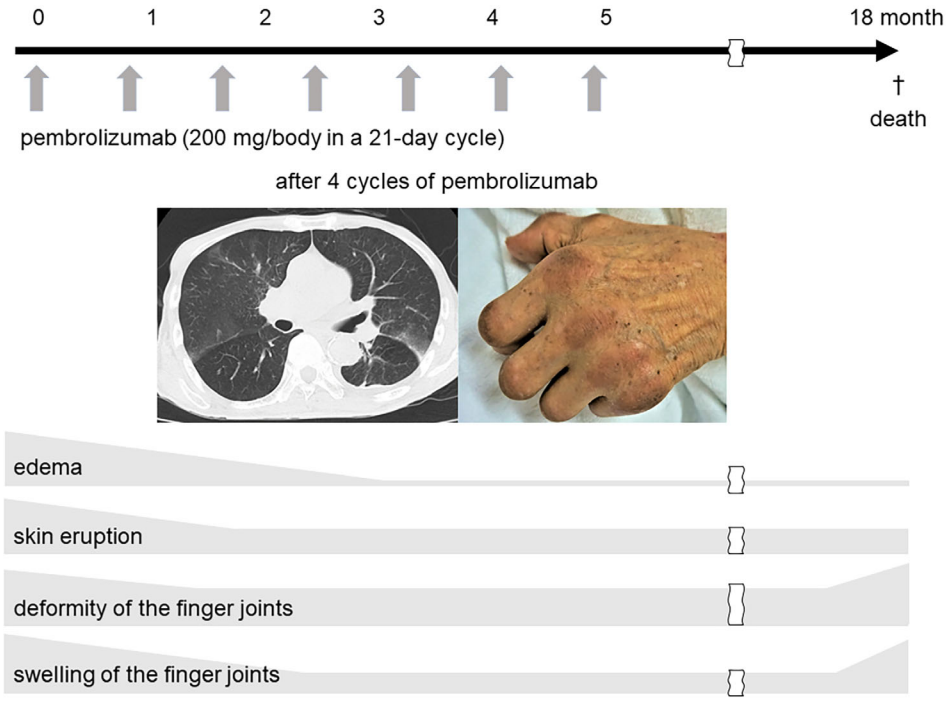

Figure 4. **Clinical course of the lung cancer and paraneoplastic syndromes. After treatment with pembrolizumab, the skin eruption, pitting edema, and swelling of the finger joints were gradually relieved, along with shrinking of the lung cancer. Deformities of the finger joints showed only small improvement. After discontinuing pembrolizumab, the swelling and deformities of the finger joints gradually worsened along with regrowth of the tumor lesions. In contrast, the pitting edema and skin eruption remained the same.**

RS3PE syndromes without elevation of CRP or MMP-3 (10, 11). Second, the deformities of the DIP joints were unusual in this case of RS3PE syndrome, and the deformities of the finger joints were suggestive of palmar fasciitis and polyarthritis syndrome (PFPAS), which is an uncommon paraneoplastic syndrome characterized by rapidly developing bilateral arthritis of the hands and fasciitis of the palms (12, 13). However, pitting edema on the extremities was not explicable by PFPAS. Therefore, in the current case, the deformities of the finger joints were considered an atypical presentation of RS3PE syndrome.

There are few reports of the simultaneous occurrence of Bazex and RS3PE syndromes. The precise mechanisms underlying each of these syndromes are unknown. However, they are both paraneoplastic syndromes that are thought to be associated with inflammatory cytokines or autoimmunity provoked by cancer (14, 15). As such, there may have been some overlap in the mechanisms underlying the two paraneoplastic syndromes in this case.

In the current case, the course of some symptoms did not completely parallel the remission and regrowth of the tumor. The reasons for the heterogeneous course of the symptoms are unknown. The deformities of the finger joints, the most severe symptom, might have become partially irreversible and therefore responded poorly to the remission of the tumor. In contrast, the pitting edema of the legs and skin eruptions did not worsen even after the regrowth of the tumor.

Immune checkpoint inhibitors (ICIs) might have modified the immune response associated with the paraneoplastic syndromes. Recently, ICIs have been widely used in cancer therapy, including lung cancer (16-18). However, ICIs are known to exacerbate preexisting autoimmune disease (19, 20). Paraneoplastic syndromes are treatable with cancer therapy. Therefore, it is important to distinguish a paraneoplastic syndrome associated with autoimmune-like symptoms from "true" autoimmune diseases before initiating ICI therapy.

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

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References

1. Bazex A, Griffiths A. Acrokeratosis paraneoplastica - a new cutaneous marker of malignancy. Br J Dermatol **103**: 301-306, 1980.
2. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. Remitting seronegative symmetrical synovitis with pitting edema: RS3PE syndrome. JAMA **254**: 2763-2767, 1985.
3. Chung VQ, Moschella SL, Zembowicz A, Liu V. Clinical and pathologic findings of paraneoplastic dermatoses. J Am Acad Dermatol **54**: 745-762, 2006.
4. Karabulut AA, Sahin S, Sahin M, Ekşioğlu M, Ustün H. Paraneoplastic acrokeratosis of Bazex (Bazex's syndrome): report of a female case associated with cholangiocarcinoma and review of the published work. J Dermatol **33**: 850-854, 2006.
5. Räßler F, Goetze S, Elsner P. Acrokeratosis paraneoplastica (Bazex syndrome) - a systematic review on risk factors, diagnosis, prognosis and management. J Eur Acad Dermatol Venereol **31**: 1119-1136, 2017.
6. Sibilia J, Friess S, Schaeverbeke T, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE): a form of paraneoplastic polyarthritis? J Rheumatol **26**: 115-120, 1999.
7. Olivé A, del Blanco J, Pons M, Vaquero M, Tena X. The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema. The Catalán Group for the Study of RS3PE. J Rheumatol **24**: 333-336, 1997.
8. Suzuki K, Shiono S, Hayasaka K, Yarimizu K, Endoh M, Yanagawa N. A surgical case of minimally invasive adenocarcinoma associated with remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome. Jpn J Lung Canc **58**: 105-110, 2018.
9. Arima K, Origuchi T, Tamai M, et al. RS3PE syndrome presenting as vascular endothelial growth factor associated disorder. Ann Rheum Dis **64**: 1653-1655, 2005.
10. Hamanaka R, Murakami S, Yokose T, Nakayama H, Yamada K, Iwazaki M. Lung cancer associated with remitting seronegative symmetrical synovitis with pitting edema-like features. Jpn J Lung Canc **51**: 253-258, 2011.
11. Origuchi T, Arima K, Kawashiri S, et al. Nine cases of remitting seronegative symmetrical synovitis with pitting edema syndrome complicated with malignancies. Clin Rheumatol **24**: 206-214, 2012.
12. Medsger TA, Dixon JA, Garwood VF. Palmar fasciitis and polyarthritis associated with ovarian carcinoma. Ann Intern Med **96**: 424-431, 1982.
13. Manger B, Schett G. Palmar fasciitis and polyarthritis syndrome - Systematic literature review of 100 cases. Nat Rev Rheumatol **44**: 105-111, 2014.
14. Iwanami K, Nakai M, Kitamura K. Bazex syndrome. Intern Med **57**: 1501-1502, 2018.
15. Arima K, Origuchi T, Tamai M, et al. RS3PE syndrome presenting as vascular endothelial growth factor associated disorder. Ann Rheum Dis **64**: 1653-1655, 2005.
16. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med **375**: 1823-1833, 2016.
17. Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol **33**: 2004-2012, 2015.
18. Metro G, Ricciuti B, Brambilla M, et al. The safety of nivolumab for the treatment of advanced non-small cell lung cancer. Expert Opin Drug Saf **16**: 101-109, 2017.
19. Califano R, Lal R, Lewanski C, et al. Patient selection for anti-PD-1/PD-L1 therapy in advanced non-small-cell lung cancer: implications for clinical practice. Future Oncol **14**: 2415-2431, 2018.
20. Leonardi GC, Gainor JF, Altan M, et al. Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. J Clin Oncol **36**: 1905-1912, 2018.