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...
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).
### Table. Laboratory Data.

| Parameter | Value               |
|-----------|---------------------|
| WBCs      | 6.32×10^3 /μL       |
| RBCs      | 474×10^4 /μL        |
| Hb        | 13.7 g/dL           |
| Hct       | 42.4 %              |
| Plt       | 20.2×10^4 /μL       |
| TP        | 6.9 g/dL            |
| Alb       | 3.5 g/dL            |
| T.bil     | 0.4 mg/dL           |
| AST       | 19 IU/L             |
| ALT       | 10 IU/L             |
| LDH       | 207 IU/L            |
| ALP       | 10 IU/L             |
| γ-GT      | 25 IU/L             |
| CK        | 60 IU/L             |
| BUN       | 13.1 mg/dL          |
| Cr        | 0.41 mg/dL          |
| CRP       | 0.1 mg/dL           |
| ESR       | 12 mm/h             |
| NT-proBNP | 264 pg/mL           |
| 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 18F-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).
cancer therapy.

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) during cancer therapy.

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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 cuta-

neous marker of malignancy. Br J Dermatol 103: 301-306, 1980.

2. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. Remitting serone-
gerative symmetrical synovitis with pitting edema: RS3PE syn-
drome. JAMA 254: 2763-2767, 1985.

3. Chung VQ, Moschella SL, Zembowicz A, Liu V. Clinical and pa-
thologic findings of paraneoplastic dermatoses. J Am Acad Derma-
tol 54: 745-762, 2006.

4. Karabulut AA, Sahin S, Sahin M, Eksicio glu M, Ustun H. Paraneo-
plastic acrokeratosis of Bazex (Bazex’s syndrome): report of a fe-
male case associated with cholangiocarcinoma and review of the published work. J Dermatol 33: 850-854, 2006.

5. Rüffer F, Goethe S, Elsner P. Acrokeratosis paraneoplastica (Bazex syndrome) - a systematic review on risk factors, diagnosis, prog-
nosis 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. Olave A, del Blanco J, Pons M, Vaquero M, Tena X. The clinical spectrum of remitting seronegative symmetrical synovitis with pit-
ting edema. The Catalan Group for the Study of RS3PE. J Rheu-
matol 24: 333-336, 1997.

8. Suzuki K, Shiono S, Hayasaka K, Yarimizu K, Endoh M, Yanagawa N. A surgical case of minimally invasive adenocarcino-

noma 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. Medsgaer TA, Dixon JA, Garwood VF. Palmar fasciitis and polyar-

thritis 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 can-
cer. 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 ad-
vanced 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: im-
lications for clinical practice. Future Oncol 14: 2415-2431, 2018.

20. Leonard 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.

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