

[ CASE REPORT ]

## Palmar Fasciitis and Polyarthrititis Syndrome Associated with Lung Adenocarcinoma

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### Abstract:

Palmar fasciitis and polyarthrititis syndrome (PPFAS) is a rare paraneoplastic rheumatic disease with characteristic features. We herein report a 77-year-old man with lung adenocarcinoma and contralateral pulmonary metastasis receiving chemotherapy who presented with progressive symmetrical flexion contractures associated with palmar fascial thickening and arthritis of both hands and shoulders. He was diagnosed with PPFAS as paraneoplastic manifestations. Salazosulfapyridine was not effective, but 15 mg/day of oral prednisolone improved his symptoms. Physicians should consider PPFAS and rule out malignancy in patients with arthritis in the extremities and flexion contractures associated with palmar fascial thickening.

**Key words:** palmar fasciitis and polyarthrititis syndrome, paraneoplastic syndrome, lung adenocarcinoma

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### Introduction

Palmar fasciitis and polyarthrititis syndrome (PPFAS) is a paraneoplastic syndrome characterized by arthritis of the proximal interphalangeal and metacarpophalangeal joints, wrists, and shoulders, swelling of the fingers, and flexion contractures associated with palmar fascial thickening, known as “woody hands” (1). Medsger et al. first reported six cases of PPFAS-associated ovarian carcinoma in 1982 (2). Although Bremer reported a case of reflex sympathetic dystrophy associated with ovarian cancer in 1967 (3), the pathophysiology of PPFAS was not recognized until the report of Medsger et al. PPFAS is a rare paraneoplastic condition, and Manger et al. reviewed 100 reported PPFAS cases in 2014 (4). Diagnosing PPFAS early is crucial, as overlooking any underlying malignancy must be avoided.

We herein report a 77-year-old man with lung adenocarcinoma receiving chemotherapy who presented with progressive flexion contractures of both hands associated with palmar fascial thickening and arthritis of both hands and shoulders. We also review the process of the diagnosis and treatment of PPFAS from the previous literature.

### Case Report

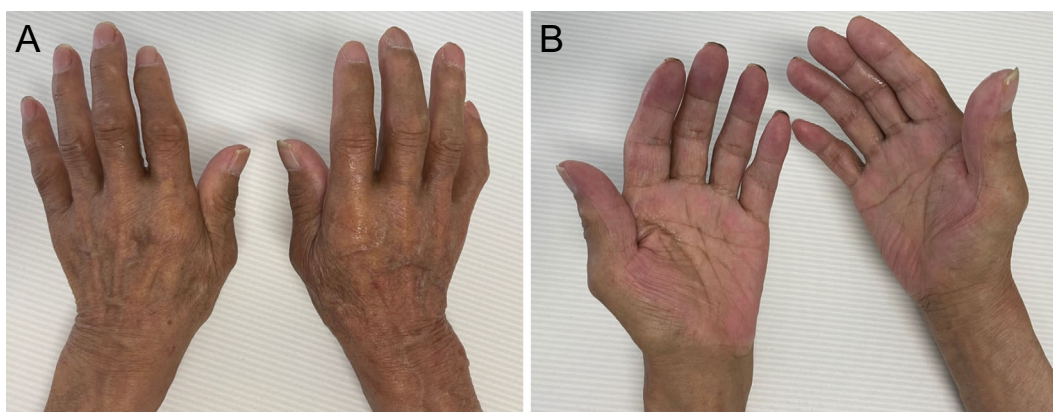
A 77-year-old Japanese man with lung adenocarcinoma presented with progressive symmetrical flexion contractures and arthritis of both hands and shoulders. He had been diagnosed with stage IV lung adenocarcinoma originating in the right upper lobe with contralateral pulmonary metastasis six months earlier. He had been started on pemetrexed for lung adenocarcinoma two months earlier. Subsequently, he recognized flexion contractures of both hands and joint pains of both hands and shoulders. A month previously, rheumatoid arthritis had been suspected, and he had been started on 1,000 mg/day of salazosulfapyridine. He was no longer able to hold chopsticks or spoons. He was admitted to the hospital for a close examination and treatment.

He denied a fever, weakness, dysphagia, prolonged morning stiffness, edema of both dorsa of the hands, or Raynaud's phenomenon. His medical history was significant for asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome. His medication included 1,000 mg/day of salazosulfapyridine, 500 mg/day of acetaminophen, 25 mg/day of diclofenac sodium suppository, 20 mg/day of esomeprazole, and inhaled vilanterol trifenatate/fluticasone furoate.

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**Figure 1.** Swelling of the distal interphalangeal, proximal interphalangeal, and metacarpophalangeal joints of both hands (A) and erythema in the thenar, hypothenar, and finger pulps and groove signs caused by deepening of the palmar crease (B) were noted. The patient had significant flexion contractures of both hands and hard palmar fascial thickening, known as “woody hands.”

He had a 47-pack-year history of cigarette smoking. He had drunk a glass of Japanese sake every day but had quit drinking it four months earlier.

On an examination, the temperature was 36.5°C, blood pressure 108/66 mmHg, pulse 64 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 96% while breathing ambient air. He had significant symmetrical flexion contractures of both hands and hard palmar fascial thickening. Swelling and tenderness of the distal interphalangeal, the proximal interphalangeal, and the metacarpophalangeal joints of both hands (Fig. 1A) and tenderness of the shoulder joints were significant. Erythema in the thenar eminences, hypothenar eminences, and finger pulps and groove sign caused by deepening of the palmar crease were noted (Fig. 1B). No clubbing, sclerodactyly, telangiectasia, periungual erythema, nail fold bleeding, Gottron’s sign, or mechanic’s hand was evident. Other physical examination findings were unremarkable.

Laboratory values were as follows: leukocyte count 10,400/ $\mu$ L (86.5% neutrophils, 7.5% lymphocytes, 2.4% monocytes, 2.1% eosinophils, 0.4% basophils, 1.1% large unstained cells); hemoglobin 10.6 g/dL; platelet count 336,000/ $\mu$ L; aspartate aminotransferase (AST) 28 U/L; alanine aminotransferase (ALT) 15 U/L; lactate dehydrogenase (LDH) 237 U/L (normal 124-222 U/L); creatine kinase (CK) 80 U/L (normal 56-244 U/L); creatinine 0.59 mg/dL; C-reactive protein (CRP) 2.6 mg/dL (normal <0.3 mg/dL); erythrocyte sedimentation rate 38 mm/h; serum IgG 900 mg/dL; IgA 331 mg/dL; IgM 123 mg/dL; total functional hemolytic complement (CH50) 52.8 U/mL (normal 25-48 U/mL); C3 121 mg/dL (normal 86-160 mg/dL); C4 21 mg/dL (normal 17-45 mg/dL); matrix metalloproteinase-3 (MMP-3) 215.9 ng/mL (normal 37-121 ng/mL); thyroid-stimulating hormone (TSH) 0.895  $\mu$ IU/mL (normal 0.50-5.0  $\mu$ IU/mL); and free thyroxine (FT4) 1.01 ng/dL (normal 0.93-1.70 ng/dL). Antinuclear antibodies were positive at a low titer value of 1:40 with a speckled pattern. Rheumatoid factor, anti-cyclic citrullinated peptide antibodies, anti-Scl-70 antibody,

and anti-U1-ribonucleoprotein (RNP) antibody were all negative.

X-ray of the hands revealed findings of moderate osteoarthritis and no evidence of erosion (Fig. 2). T1-weighted magnetic resonance imaging (MRI) of the hands showed evidence of high signal intensity around the flexor and extensor tendons but no synovitis or bone marrow edema (Fig. 3A). Gadolinium-enhanced T1-weighted MRI of the hands demonstrated diffuse enhancement in the fascia, flexor tendons, and extensor tendons (Fig. 3B).

Based on the above findings, he was diagnosed with PFPAS as paraneoplastic manifestations of lung adenocarcinoma with metastasis.

Administration of salazosulfapyridine was discontinued because of a lack of improvement. On day 5, oral prednisolone 15 mg daily was initiated. His arthritis and flexion contractures of both hands gradually improved, and he was able to hold chopsticks and spoons again. Furthermore, after the initiation of chemotherapy, his lung adenocarcinoma showed gradual improvement on diagnostic imaging, while the tumor marker carcinoembryonic antigen (CEA) decreased. On day 40, his arthritis of both hands had disappeared, but his flexion contractions persisted (Fig. 4). On day 140, follow-up gadolinium-enhanced T1-weighted MRI showed reduced enhancement in the fascia, flexor tendons, and extensor tendons (Fig. 3C).

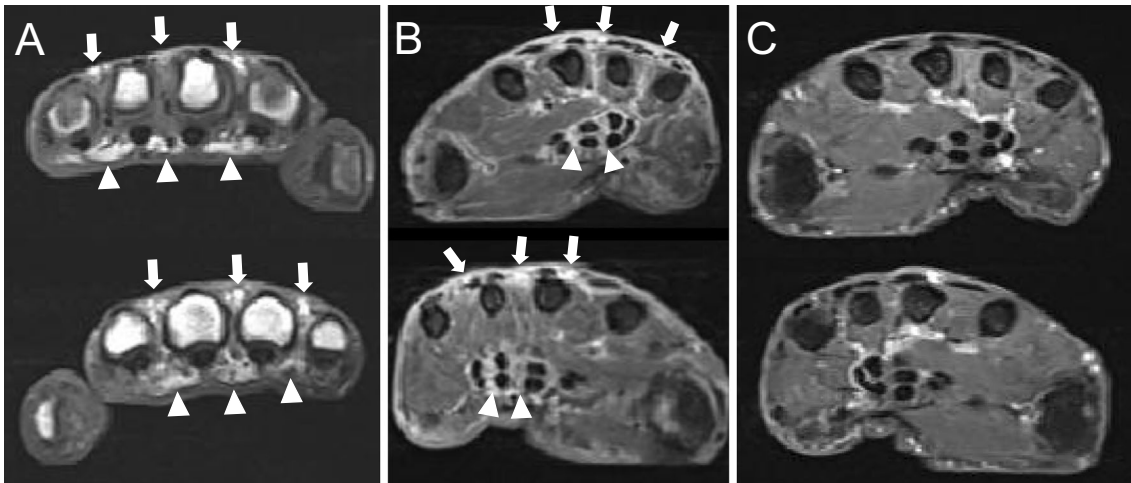
## Discussion

PFPAS is a rare paraneoplastic rheumatic disease characterized by arthritis of the proximal interphalangeal and metacarpophalangeal joints and wrists, and swelling of the fingers, palmar fascial thickening, and flexion contractures. Other involved joints include the shoulders, elbows, knees, and ankles (4).

Manger et al. reviewed reported cases with PFPAS (4). These cases had been associated with various malignancies, such as ovary, prostate, breast, lung, pancreas, colon, as well



**Figure 2.** X-ray of hands disclosed findings of moderate osteoarthritis and no evidence of erosion.



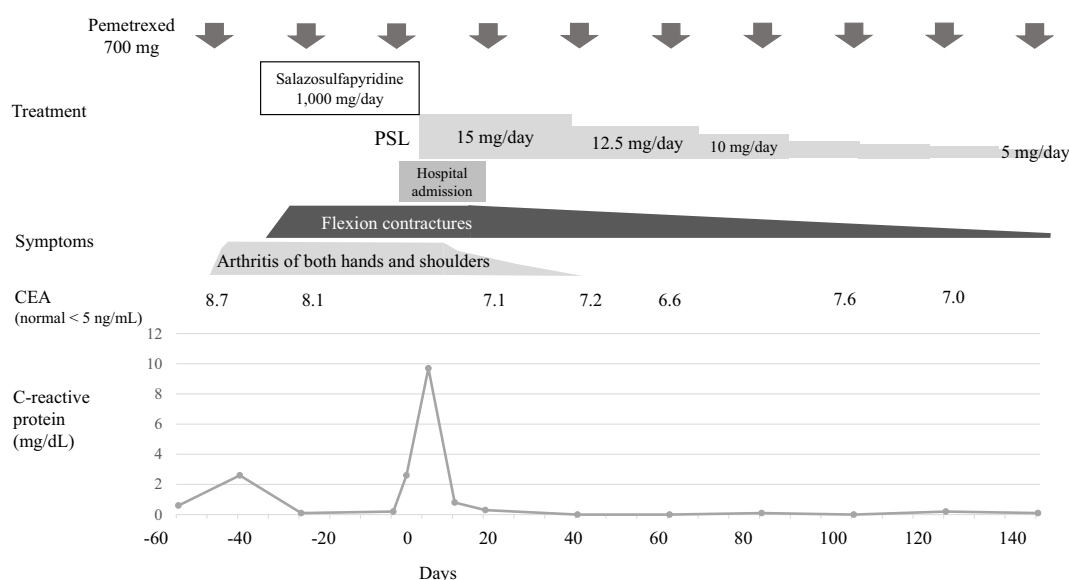
**Figure 3.** T1-weighted imaging (A, upper: right, lower: left) of hands showed evidence of a high signal intensity around the flexor tendons (arrowheads) and extensor tendons (arrows) but no synovitis or bone marrow edema. Gadolinium-enhanced T1-weighted MRI (B, upper: right, lower: left) of hands demonstrated diffuse enhancement in the fascia, flexor tendons (arrowheads), and extensor tendons (arrows). Follow-up gadolinium-enhanced T1-weighted MRI (C, upper: right, lower: left) of hands showed decreased enhancement in the fascia, flexor tendons, and extensor tendons.

as hematological malignancies including chronic lymphatic lymphoma, Hodgkin's lymphoma, plasmacytoma of thyroid gland, and multiple myeloma. The most common histological type was adenocarcinoma. Ovarian adenocarcinoma was the most frequent type of malignancy (36.8%; 32/87 patients), and gastrointestinal organ tumors were the second-most frequent type (19.6%; 17/87 patients). Lung cancer was an infrequent type of malignancy (6.9%; 6/87 patients). To our knowledge, seven cases of PFPAS associated with lung cancer have been reported: four cases had non-small cell carcinoma, two had small-cell carcinoma, and one had adenocarcinoma (4, 5).

The pathogenic mechanism of PFPAS is still unknown.

Transforming growth factor  $\beta$  (TGF- $\beta$ ) and connective tissue growth factor have been implicated as fibroblast-proliferative factors (6). Ovarian cancer releases cytokines, such as vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and TGF- $\beta$  (7). Considering the association with ovarian cancer, these cytokines are thought to play an important role in the progression of PFPAS. The expression of TGF- $\beta$ , IGF, and VEGF is also found in lung cancer (8-10), and TGF- $\beta$  is associated with metastasis of lung cancer (8).

PFPAS should be considered in cases of acute- or subacute-onset symmetrical flexion contractures of both hands and polyarthritis, particularly with seronegativity and



**Figure 4.** The clinical course of the patient. PSL: prednisolone

in the absence of Raynaud's phenomenon (11), as the combination of seronegative arthritis and the absence of Raynaud's phenomenon is atypical for rheumatoid arthritis, scleroderma, mixed connective tissue disease, and systemic lupus erythematosus. The diagnosis of PFPAS is based on clinical symptoms and physical examinations. Characteristically, PFPAS causes painful swelling of the fingers, flexion contractures associated with palmar fascial thickening, which are known as "woody hands" (1). Although the information from skin biopsies and MRI is helpful, these findings do not permit a definite diagnosis of PFPAS (4). Although PFPAS is rare, physicians should diagnose PFPAS early and consider the possibility of underlying malignancy.

The differential diagnoses of PFPAS include rheumatoid arthritis, scleroderma, reflex sympathetic dystrophy, eosinophilic fasciitis, diabetic cheiroarthropathy, and Dupuytren's contracture. Reflex sympathetic dystrophy, known as complex regional pain syndrome, causes chronic burning pain, characteristically affecting one extremity, and it often shows up after medical procedures or trauma (12). Eosinophilic fasciitis, also called Shulman syndrome, is characterized by fascial thickening with eosinophilic infiltration, peripheral eosinophilia, and hypergammaglobulinemia (13). Diabetic cheiroarthropathy is characterized by flexion contracture of the fingers and sclerosis of tendons, usually in poorly controlled diabetes mellitus (14).

Recently, immune checkpoint inhibitors have been commonly used in cancer immunotherapy but have induced immune-related adverse events (irAEs) in some cases. A wide spectrum of rheumatologic irAEs has been reported. A multicenter cohort study reported that systematic polyarthritis was the most frequent rheumatologic irAE (15). Other rheumatologic irAEs include polymyalgia rheumatic-like syndromes, psoriatic arthritis, remitting seronegative symmetrical synovitis with pitting edema (RS3PE), tenosynovitis, vasculitis, myositis, scleroderma, and eosinophilic fasciitis (16-18).

Paraneoplastic syndromes are important differential diagnoses of rheumatologic irAEs (16), and the distinction between paraneoplastic syndromes and rheumatologic irAEs under immunotherapy is difficult in some cases. Shibata et al. reported a case of paraneoplastic dermatomyositis after nivolumab administration for gastric cancer (19). PFPAS associated with immunotherapy has not yet been reported. However, we should consider PFPAS as a paraneoplastic syndrome or rheumatologic irAE when a patient on immunotherapy has palmar fasciitis and arthritis in the extremities in this era.

At the onset of PFPAS, the tumor has already advanced to a late stage of metastatic spread in most reported cases (4). Musculoskeletal symptoms precede the tumor diagnosis in approximately 70% of patients with PFPAS (4). In some patients, the tumor diagnosis had already been made when musculoskeletal symptoms appeared (4). Therefore, the outcome of patients with PFPAS is generally unfavorable. In our case, musculoskeletal symptoms appeared after the diagnosis of lung cancer.

Treatment of PFPAS involves treating the underlying neoplasm and administering immunosuppressive medications. Corticosteroids and disease-modifying antirheumatic drugs are often used, although the effect is limited (4). The early diagnosis and treatments are crucial for improving the contractures and arthritis, and antineoplastic treatment, including excision of the tumor, can help manage musculoskeletal symptoms. Enomoto et al. reported a case of PFPAS associated with gastric carcinoma that showed complete resolution of musculoskeletal symptoms after curative tumor resection (20). In our case, the patient was diagnosed with PFPAS relatively early after the musculoskeletal symptoms appeared, and prompt treatment was initiated, which resulted in improvement of both the polyarthritis and hand function. However, the effect on flexion contractures in both hands was insufficient. In addition to the treatment of his muscu-



loskeletal symptoms by corticosteroid and chemotherapy for lung cancer might provide additional improvement of his musculoskeletal symptoms.

In conclusion, PFPAS is a rare paraneoplastic syndrome characterized by arthritis of the proximal interphalangeal and metacarpophalangeal joints, wrists, and shoulders, swelling of the fingers, and flexion contractures associated with palmar fascial thickening. Physicians should consider PFPAS and rule out malignancy when a patient has arthritis in the extremities and flexion contractures associated with palmar fascial thickening.

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

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#### References

- Alexandroff AB, Hazleman BL, Matthewson M, et al. Woody hands. *Lancet* **361**: 1344, 2003.
- Medsger TA, Dixon JA, Garwood VF. Palmar fasciitis and polyarthritis associated with ovarian carcinoma. *Ann Intern Med* **96**: 424-431, 1982.
- Bremer C. Shoulder-hand syndrome. A case of unusual aetiology. *Ann Phys Med* **9**: 168-171, 1967.
- Manger B, Schett G. Palmar fasciitis and polyarthritis syndrome-systematic literature review of 100 cases. *Semin Arthritis Rheum* **44**: 105-111, 2014.
- Lazarev I, Shelef I, Refaely Y, Ariad S, Ifergane G. Two paraneoplastic autoimmune syndromes: limbic encephalitis and palmar fasciitis in a patient with small cell lung cancer. *Rare Tumors* **7**: 5721, 2015.
- Clarke LL, Kennedy CT, Hollingworth P. Palmar fasciitis and polyarthritis syndrome associated with transitional cell carcinoma of the bladder. *J Am Acad Dermatol* **64**: 1159-1163, 2011.
- Kajikawa H, Sobajima T, Koiwai C, Ichigo S, Takagi H, Imai A. Palmar fasciitis with polyarthritis-associated ovarian cancer: case report and literature review. *Mol Clin Oncol* **8**: 292-295, 2018.
- Li J, Shen C, Wang X, et al. Prognostic value of TGF- $\beta$  in lung cancer: systematic review and meta-analysis. *BMC Cancer* **19**: 691, 2019.
- Velcheti V, Govindan R. Insulin-like growth factor and lung cancer. *J Thorac Oncol* **1**: 607-610, 2006.
- Jung WY, Min KW, Oh YH. Increased VEGF-A in solid type of lung adenocarcinoma reduces the patients' survival. *Sci Rep* **11**: 1321, 2021.
- Mahoney K, Cayea D, Li QK, Gelber AC. A handy clue: palmar fasciitis and polyarthritis syndrome. *Am J Med* **127**: 116-118, 2014.
- Bruehl S. Complex regional pain syndrome. *BMJ* **351**: h2730, 2015.
- Pinal-Fernandez I, Selva-O'Callaghan A, Grau JM. Diagnosis and classification of eosinophilic fasciitis. *Autoimmun Rev* **13**: 379-382, 2014.
- Cherqaoui R, McKenzie S, Nunlee-Bland G. Diabetic cheiroarthropathy: a case report and review of the literature. *Case Rep Endocrinol* **2013**: 257028, 2013.
- Roberts J, Ennis D, Hudson M, et al. Rheumatic immune-related adverse events associated with cancer immunotherapy: a nationwide multi-center cohort. *Autoimmun Rev* **19**: 102595, 2020.
- Kostine M, Finckh A, Bingham CO, et al. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. *Ann Rheum Dis* **80**: 36-48, 2021.
- Barbosa NS, Wetter DA, Wieland CN, Shenoy NK, Markovic SN, Thanarajasingam U. Scleroderma induced by pembrolizumab: a case series. *Mayo Clin Proc* **92**: 1158-1163, 2017.
- Chan KK, Magro C, Shoushtari A, et al. Eosinophilic fasciitis following checkpoint inhibitor therapy: four cases and a review of literature. *Oncologist* **25**: 140-149, 2020.
- Shibata C, Kato J, Toda N, et al. Paraneoplastic dermatomyositis appearing after nivolumab therapy for gastric cancer: a case report. *J Med Case Rep* **13**: 168, 2019.
- Enomoto M, Takemura H, Suzuki M, et al. Palmar fasciitis and polyarthritis associated with gastric carcinoma: complete resolution after total gastrectomy. *Intern Med* **39**: 754-757, 2000.

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