

CASE REPORT

Hypertrophic pulmonary osteoarthropathy due to lung cancer: A case report and literature review

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Abstract

Hypertrophic pulmonary osteoarthropathy (HPOA) is a rare paraneoplastic syndrome. Our literature review shows the location of arthralgia and existence of edema are referable information for the differential diagnosis in paraneoplastic arthralgia.

KEYWORDS

anti-cyclic citrullinated peptide antibody, arthralgia, edema, hypertrophic pulmonary osteoarthropathy, lung cancer, paraneoplastic

1 | INTRODUCTION

Hypertrophic pulmonary osteoarthropathy (HPOA), also known as Marie-Bamberger syndrome, is a rare paraneoplastic syndrome characterized by the classic triad of clubbed fingers, periostosis of the long tubular bones, and arthralgia.¹ The most common cause of HPOA is lung cancer, specifically adenocarcinoma; therefore, HPOA is considered a paraneoplastic syndrome.² However, since remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is often included as a differential diagnosis in patients with paraneoplastic arthralgia,³ it is important for physicians to understand the clinical features of HPOA to identify, diagnose, and treat HPOA appropriately. Herein, we report a case of HPOA in a stage IV nonsmall cell lung cancer patient, with a literature review of HPOA cases due to lung cancer in Japan and comparison of the clinical characteristics of lung cancer associated with HPOA and RS3PE.

2 | CASE PRESENTATION

A 49-year-old woman current smoker visited another clinic with a 1-week history of swelling in the extremities. Chest X-ray revealed a mass in the left upper lung field (Figure 1), for which she was referred to our hospital. Clubbed fingers and pitting edema in the extremities were noted on admission. The main laboratory findings on admission were as follows: white blood count, 8200 cells/ μ L; total protein, 6.3 g/dL; albumin, 2.5 g/dL; and creatinine, 0.48 mg/dL. Urinalysis including urinary sediment was within normal range, and there was no proteinuria. She tested negative for lung cancer tumor markers such as carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA), and pro-gastrin releasing peptide (Pro-GRP). Chest computed tomography (CT) revealed a 9-cm mass in the upper lobe of the left lung, swelling of the left mediastinal lymph nodes, multiple lung nodules, and left pleural dissemination and effusion. Enhanced abdominal CT, enhanced



FIGURE 1 Chest X-ray on admission. A large mass was seen in the left upper lung field. Left main bronchus and left hilum were compressed downward by huge mass. In addition, left pleural effusion was seen

brain magnetic resonance imaging, and positron-emission tomography revealed no abnormality in other organs. The maximum standardized uptake value (SUVmax) for the lung mass was 24.20. Upper gastrointestinal tract endoscopy detected only atrophic gastritis. We initially performed transbronchial lung biopsy but confirmed diagnosis was not obtained. Biopsy of the mediastinal lymph node via endoscopic ultrasound-guided fine needle aspiration performed on the other day indicated poorly differentiated nonsmall cell lung cancer (suspected as adenocarcinoma). Finally, she was diagnosed with stage IV (cT4N2M1a) lung cancer, with negative results for *EGFR* and *ALK* mutations.

On day 8 after admission, she complained of acute joint pain in both knees, ankles, and elbows. Hand radiography revealed no erosion or destruction in any of the joints. Owing to pitting edema, RS3PE was initially suspected; however, RS3PE was eliminated as a differential diagnosis because of elevated levels of serum rheumatoid factor (RF) [33 IU/mL] and anti-cyclic citrullinated peptide antibody (anti-CCP Ab) [14.7 U/mL]. Rheumatoid arthritis (RA) was also not considered because the acute onset of arthralgia was not typical of RA, and her symptoms and findings did not satisfy the diagnostic criteria of RA described by the American College of Rheumatology/European League Against Rheumatism in 2010.⁴ Bone scintigraphy revealed linear accumulation of radioactive tracer along the surface of the tibial and peroneal bones on both sides (Figure 2). Finally, HPOA was diagnosed based on the patient's symptoms and because the scintigraphy findings fulfilled the diagnostic criteria of HPOA.



FIGURE 2 Bone scintigraphy. Linear accumulation of radioactive tracer along the surface of the tibial and peroneal bones on both sides was seen

Additionally, a monolayer lesion was observed between the diaphyseal and epiphyseal regions in the four long bones; thus, the severity of HPOA was classified as mild. She received best supportive care only by her strong will and was discharged on day 20 after admission.

3 | DISCUSSION

Bamberger and Marie reported the first case of HPOA in the 1890s, and the three findings of clubbed fingers, periosteal reaction of the long tubular bones, and arthralgia were needed for the diagnosis.^{1,5,6} However, in 1992, physicians at the International Meeting on Hypertrophic Osteoarthropathy agreed that arthralgia was not necessary for a diagnosis of HPOA, and the severity was classified as mild, moderate, or severe based on the extent of the periosteal reaction.⁷ The current case fulfilled the classic triad findings and was diagnosed as mild HPOA.

Although the current patient did not have RA, her serum was positive for both RF and anti-CCP Ab. To the best of our knowledge, a case of HPOA with elevated serum anti-CCP Ab has not yet been reported. Anti-CCP Ab is produced during

TABLE 1 Characteristics of lung cancer cases associated with hypertrophic pulmonary osteoarthropathy in Japan

	Number of patients (%)		Number of patients (%)
Total	101	Primary tumor site	92
Median age, y [range]	57 [35-78]	Central	12 (13.0%)
Male gender	88 (87.1%)	Peripheral	80 (87.0%)
Symptoms	101	Stage	76
Arthralgia	101 (100%)	I	23 (30.3%)
Site of arthralgia		II	8 (10.5%)
Upper limb	36 (35.6%)	III	28 (36.8%)
Lower limb	85 (84.2%)	IV	17 (22.4%)
Trunk	14 (13.9%)	Treatment	101
Leg edema	25 (24.8%)	Surgery	58 (57.4%)
Histology	94	Radiation	23 (22.8%)
Ad	60 (63.8%)	Chemotherapy	38 (37.6%)
Sq	15 (16.0%)	BSC	6 (5.9%)
Sm	2 (2.1%)	Change in arthralgia	94
Lg	14 (15.0%)	Improvement	83 (88.3%)
NSCLC	3 (3.2%)	Worsening	2 (2.1%)
		No change	9 (9.6%)

Abbreviations: Ad, adenocarcinoma; BSC, best supportive care; Lg, large cell carcinoma; NSCLC, nonsmall cell lung cancer; Sm, small cell carcinoma; Sq, squamous cell carcinoma.

synovial inflammation in patients with RA, and the specificity of anti-CCP Ab for RA diagnosis reaches 98%; hence, anti-CCP Ab is often used for diagnosing RA.⁸ However, anti-CCP Ab is sometimes elevated in patients without RA,⁹⁻¹² and Baka et al reported that 5.9% of patients with lung cancer were positive for serum anti-CCP Ab.¹¹ They performed immunostaining for 141 lung cancer tissues and reported that all the samples were positive for citrullinated protein.¹¹ Baka et al speculated that activated immune cells by cancer inflammation produce citrullinated protein and transient RF in the lungs, both of which can be enhanced by smoking. However, this process may be insufficient to induce immune reactions against citrullinated protein because serum levels of anti-CCP Ab were elevated in only a small subset of patients with lung cancer. They suggested a hypothesis that antibodies against these citrullinated proteins may be produced in patients with a genetic predisposition, such as those with alleles of HLA-DRB1.¹¹ However, it is well known that only a limited number of inflammatory cells are observed in the synovial fluid of patients with HPOA.¹³ Taken together, we speculate that the elevation of the anti-CCP Ab levels in this case might be due to the immune reaction to the citrullinated protein in lung cancer tissue, possibly enhanced by smoking, although we did not evaluate the presence of HLA-DRB1 alleles.

Although some studies have investigated the characteristics of HPOA cases in Japan, the number of enrolled patients in most studies was relatively small; also, patients enrolled in older studies were not strictly selected according

to the diagnostic criteria of HPOA.¹⁴⁻¹⁶ Recently, Miyata et al summarized 71 cases of lung cancer-associated HPOA in Japan from 1983 to 2012.¹⁷ However, the clinical characteristics such as the site of arthralgia and existence of edema were not mentioned in most previous studies. Therefore, in the current study, to determine the clinical characteristics of HPOA in Japanese lung cancer patients, we performed a literature review of cases of HPOA due to lung cancer in Japan—that fulfilled the diagnostic criteria of HPOA—reported in English or Japanese between 1960 and 2018. We found 101 cases including the current case (Table 1). The median patient age was 57 years, and 87.1% of patients were men. Adenocarcinoma was the most common histology (59.4%), and the primary lesion was most commonly observed in the peripheral lung field (87.0%) rather than in the central field. There was no predominance regarding the clinical stage of lung cancer. Arthralgia was more common in the lower limb (84.2%) than in the upper limb (35.6%). Moreover, edema in the extremities (pitting or nonpitting) was observed in 24.8% of the patients. The presence of anti-CCP Ab was examined in only 2 cases, both of which were negative. The results of the current literature review showed that 88.3% of patients experienced amelioration of arthralgia after anticancer therapy, similar to previously reported information.¹⁸

We also reviewed previous articles that reported lung cancer cases associated with HPOA from other countries; the results are summarized in Table 2.^{14,17,19-22} The largest

TABLE 2 Representative reports of lung cancer associated with hypertrophic pulmonary osteoarthropathy

Author	Number of patients	Country	Year of publication	Median age	Male (%)	Histology (%)			Primary tumor site (%)			Stage (%)					
						Ad	Sq	Sm	Lg	Central	Peripheral	I	II	III	IV		
Segal et al ¹⁹	16	USA	1982	55.6 ^a	68.8	37.5	25	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Morgan et al ²⁰	28	UK	1996	68 ^a	78.6	12	46	15	19	56.5	43.5	NM	NM	NM	NM	NM	NM
Izumi et al ¹⁴	55	Japan	2010	64	70.9	45.5	30.9	12.7	9.1	NM	NM	10	0	70	20		
Miyata et al ¹⁷	71	Japan	2014	62	78.9	71.8	14	1.4	9.9	NM	NM	NM	NM	NM	NM	NM	NM
Qian et al ²¹	115	China	2014	62	91.3	48	23	2	3	NM	NM	16	8	47	29		
Fang et al ²²	69	China	2017	M:61, F:53	81.2	60.9	17.4	1.4	7.2	NM	NM	1.4	8.7	21.8	68.1		
Current report	101	Japan	—	57	87.1	63.8	16	2.1	14.9	13	87	30.3	10.5	36.8	22.4		

Abbreviations: Ad, adenocarcinoma; F, female; Lg, large cell carcinoma; M, male; NM, not mentioned; Sm, small cell carcinoma; Sq, squamous cell carcinoma.

^aAverage age.

study was the retrospective analysis by Qian et al²¹ The study included 115 patients; 91% of the patients were men, and the median age was 62 years. Adenocarcinoma was the most common histology (48%). Thus, the results are similar between the above-mentioned study and our study. However, the predominance of the location of arthralgia and the existence of edema were not investigated in most previous studies. Segal et al investigated the location of arthralgia in patients with HPOA and reported that 68.8% (11/16) and 87.5% (14/16) of the patients had arthralgia in the upper and lower limbs, respectively.¹⁹ Although the source of information is not described, some review articles mentioned that arthralgia was more common in the lower limbs in patients with HPOA.^{18,23}

As indicated in the current case, RS3PE is often considered in the differential diagnosis for paraneoplastic arthralgia. RS3PE is characterized by the following clinical features: (a) rheumatoid factor negativity, (b) occurrence in patients aged >50 years, (c) the presence of acute symmetrical polyarthritides, and (d) the presence of pitting edema on the dorsum of the hands and feet on both sides.²⁴ The treatment for both paraneoplastic HPOA and RS3PE is anticancer therapy; however, anticancer therapy is sometimes contraindicated in some cases. In such cases, the therapeutic approach for HPOA and RS3PE is different. Bisphosphonates or unilateral vagotomy may be alternative options for the treatment of HPOA,^{25,26} while corticosteroids are used for treating RS3PE.²⁷ Therefore, the differential diagnosis is clinically important. Although the common cause of HPOA is lung cancer, RS3PE is often caused by gastrointestinal, prostate, and hematological malignancies.²⁷ Furthermore, the absence of edema is useful to differentiate between these two diseases. If edema is not observed, RS3PE can be eliminated as a diagnosis. Furthermore, the location of arthralgia might be useful for the differential diagnosis. As mentioned above, arthralgia is often observed in the lower limbs in patients with HPOA, while arthralgia in RS3PE cases is often observed in the upper limb (91% of cases vs. 26% of cases in the lower limb).²⁸

In conclusion, we reported a case of HPOA and summarized HPOA cases in Japan. The clinical features of Japanese patients with HPOA are similar to those of patients reported from other countries. Moreover, for the differentiation of HPOA from RS3PE, the type of primary cancer, absence of edema, and location of arthralgia are useful in clinical practice.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

AS: participated in the management of this patient, performed the literature review, and wrote the manuscript. TM, SY, KK, MN, KM, and MF: participated in the management of this patient and revised the manuscript. TK and JF: wrote the manuscript and supervised the manuscript writing and literature review. All authors read and approved the final manuscript.

ETHICAL APPROVAL

Written informed consent was obtained from the patient for the publication of this case report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this report are available from the corresponding author, TK, upon reasonable request.

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