Anti-cyclic citrullinated peptide antibody-positive rheumatoid arthritis caused by bacterial organizing pneumonia in a patient with Sjogren's syndrome

TARO HORINO¹, MITSU HARU YOSHIDA¹, SATOSHI INOTANI¹, KAZUKI ANABUKI², HIROSHI OHNISHI²,
MASAHIRO KOMORI³, OSAMU ICHII⁴, YOSHIO TERADA¹

¹Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University, Japan

²Department of Hematology and Respiratory Medicine, Kochi Medical School, Kochi University, Japan

³Department of Otolaryngology, Kochi Medical School, Kochi University, Japan

⁴Laboratory of Anatomy, Department of Biomedical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Japan

A 58-year-old woman with a history of Sjogren's syndrome was admitted to our hospital with cough, decreased right lung breath sounds and arthralgia in both thumbs. Chest computed tomography showed consolidation with air bronchogram in the right lung. Levels of anti-cyclic citrullinated peptide antibody and rheumatoid factor levels were significantly elevated. She was diagnosed with rheumatoid arthritis induced by bacterial organizing pneumonia. Treatment with salazosulfapyridine was added for rheumatoid arthritis and arthralgia gradually improved. This case highlights that respiratory infections could lead to anti-cyclic citrullinated peptide antibody-positive rheumatoid arthritis in patients with Sjogren's syndrome.

Key words: anti-cyclic citrullinated peptide antibody (ACPA), bronchus-associated lymphoid tissue (BALT), organizing pneumonia (OP), rheumatoid arthritis (RA), Sjogren syndrome (SjS).

INTRODUCTION

Sjogren's syndrome (SjS) is a chronic autoimmune disease that involves exocrine glands with inflammatory infiltrates and leads to dysfunction of the salivary and lacrimal glands [1]. SjS is closely associated with other autoimmune rheumatic diseases, such as systemic lupus erythematosus and rheumatoid arthritis (RA), with a prevalence of SjS in RA patients as high as 55% [2]. Furthermore, the coexistence of RA and Sjogren's syndrome results in more severe arthritis with worse joint damage than is typical with RA alone [3]. Although the positivity of autoantibody profiles, including anti-cyclic citrullinated peptide antibody (ACPA) or rheumatoid factor (RF), in patients with primary SjS have already been investigated in other studies [4, 5], the positive conversion of disease-specific autoantibodies remains unclear.

We herein report a case of SjS with ACPA-positive rheumatoid arthritis induced by bacterial organizing pneumonia.

CASE REPORT

A 58-year-old Japanese woman presented with stiffness on both hands and arthralgia in the metacarpophalangeal (MCP) joints of both thumbs. She has no medical history of periodontitis and smoking. Five years ago, she visited our rheumatology clinic for dry mouth and fatigue and was diagnosed with SjS with anti-SSA antibody positive and prominent lymphocyte infiltration in the salivary glands on salivary gland biopsy specimen. At that time, she had no arthralgia and was negative for anti-cyclic citrullinated peptide antibody (ACPA) (<0.6 U/mL, normal range <4.5). Three months ago, she had a fever-free cough, with mildly stiffness and her ACPA changed to positive (172.0 U/mL). One month before admission, she had low grade fever and arthralgia in the MCP joints of both thumbs. Two days before admission, her arthralgia was exacerbated and the levels of C-reactive protein (CRP), rheumatoid factor (RF), matrix metalloproteinase-3 (MMP-3), and ACPA were elevated to 11.4 mg/dL (<0.15), 118.0 IU/mL (<15), 97.5 ng/mL (17.3–59.7), and 331.0 U/mL,

respectively. Therefore, she was admitted to the hospital for further examination and treatment of suspected RA.

On admission, a physical examination showed swelling of the MP joints of both thumbs and decreased breath sounds in her right lung without rales. Her height and weight were 152 cm and 40.8 kg, respectively. Her blood pressure was 130/89 mmHg and pulse was 95/min, regular. Her body temperature was 37.2°C. Laboratory tests revealed the elevated levels of CRP (10.2 mg/dL) and soluble interleukin-2 receptor (sIL-2R) (993.5 U/mL, 157–474) and the decreased levels of serum albumin (1.8 g/dL, 4.1–5.1) and hemoglobin (8.9 g/dL, 11.6–14.8). Chest X-ray showed an infiltrative shadow in the right lung, with elevated right diaphragm and right displacement of the mediastinum (Figure 1A). X-ray of her hands revealed no apparent deformation. Chest computed tomography (CT) showed the consolidation with air bronchogram and pleural effusion in the right lung and longitudinal lymphadenopathy (Figure 1B). Sputum culture was positive for *Staphylococcus*

aureus, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*. Based on these findings, she was diagnosed as RA with bacterial organizing pneumonia. Antibiotic therapy with tazobactam 1.5g/day and piperacillin 12g/day initially administrated for 12 days, following cefepime 4g/day for 8 days, and subsequently fever and cough improved and lung consolidation resolved (Figure 1C). She was discharged and antibiotics changed to oral levofloxacin 500 mg/day. One month later, since her arthralgia was persistent, so salazosulfapyridine 1000 mg/day was added for the treatment of RA. Two months later, the bronchoscope showed no obvious abnormal findings. A biopsy specimen of lung revealed fibrosis of the alveolar wall and swelling of alveolar cells (Figure 2). Her arthralgia continued and gradually worsened, spread to MCP and proximal interphalangeal (PIP) joints of both hands and both wrists, both elbows and both shoulders. Treatment of abatacept 125 mg/week was started, and subsequently her arthralgia resolved, and levels of CRP and MMP3 were normalized (Figure 3)

Figure 1. Findings of X rays of chest and chest computed tomography.

- A) Chest X-ray showing an infiltrative shadow in the right lung, with elevated right diaphragm and right displacement of the mediastinum.
- B) Chest computed tomography at hospital admission showing the consolidation with air bronchogram and pleural effusion in the right lung and longitudinal lymphadenopathy.
- C) One month after discharge, chest computed tomography showing improvement of pulmonary lesions.

Figure 2. Histological findings of the biopsy specimen of the lung.

A biopsy specimen of the lung showing fibrosis of the alveolar wall and swelling of alveolar cells.

Figure 3. Clinical course of our patient.

TAZ/PIPC: tazobactam/piperacillin, CMX: cefepime, LVFX: levofloxacin, CRP: C-reactive protein, MMP-3: matrix metalloproteinase-3, Alb: albumin, IgG: immunoglobulin G, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody.

DISCUSSION

We experienced an important case in which we were able to observe the course of RA associated with the positive conversion of ACPA and the increase in RF level triggered by bacterial organizing pneumonia in a patient with SjS. RA is a chronic autoimmune inflammatory disease that is typically characterized by joint destruction and deformities.

Autoantibodies have proven to be the most powerful predictors for development of clinical arthritis currently available. The subdivision of RA by autoantibody status, traditionally RF and more recently ACPA, has facilitated greater understanding of potential pathogenic mechanisms in the development of RA. Previous investigators have reported that individuals with both ACPA and RF have a 10.5 times higher risk of developing RA than seronegative individuals and especially, only ACPA was independently associated with development of RA [6]. Moreover, higher RF levels were reported to be associated with an increased risk of progression to clinical arthritis and with being ACPA-positive [6]. The sensitivity and specificity for ACPA were 67% and 95%, respectively, while the values for RF were 69% and 85%, respectively [7]. Therefore,

ACPA is considered to be more specific than RF for diagnosing RA [7].

Recent investigators have proposed that, especially in case for ACPA-positive RA, RA initiating sites distant from the joints could be within the gastrointestinal and respiratory systems [8]. Periodontitis increases the risk of RA in non-smokers and is associated with ACPA production [9]. A recent study demonstrated that *Porphyromonas gingivalis*, which is resident in the gastrointestinal tract and causes periodontitis, promoted the onset and progression of ACPA-positive RA [10]. Within the respiratory system, cigarette smoke is a major environmental risk factor for RA [11, 12]. Increased citrullinated peptides are found in the lung tissue of smokers [13, 14], suggesting that it is responsible for the increased prevalence of ACPA, leading to the development of ACPA-positive RA [15, 16]. Bronchus-associated lymphoid tissue (BALT) is not believed to represent a normal constituent of human lungs, but rather development is driven by long-term exposure to various antigenic stimuli [17, 18]. Inducible BALT is well developed in patients with pulmonary complications of RA or SjS, and is thought to be involved in local RA pathogenesis [19]. Furthermore, infections also

increase citrullination of peptides [20] and respiratory microorganisms are linked to the development of RA [21]. In our case, we speculated that BALT stimulated by bacterial infection may have induced an increase in ACPA, leading to the development of RA.

In our case, three species of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus pyogenes* were identified as causative organisms from sputum cultures. Unfortunately, it was not possible to determine whether the bacteria responsible for organizing pneumonia and presumed ACPA production stimulation were a

single species of these or coordinated pathogenicity. Nevertheless, sensitive antibiotic treatment improved organizing pneumonia and slowed the rate of exacerbation of RA, suggesting that these bacterial infections had some involvement in RA pathogenesis.

In conclusion, SjS often overlaps with various autoimmune diseases and is classified as secondary SjS. Our case suggested that SjS might be a precursor of various autoimmune diseases and local immune system stimulated by some infections could cause development of RA in patients with SjS.

O pacientă în vârstă de 58 de ani cu istoric de sindrom Sjogren a fost internată cu tuse, artralгии la police bilateral și scăderea murmurului vezicular drept. Analiza CT toracic a arătat consolidare cu bronhogramă aeriană la nivelul pulmonului drept. Nivelurile Ac anti CCP și ale factorului reumatoid erau crescute. Pacienta a fost diagnosticată cu artrită reumatoidă indusă de pneumonie bacteriană dreaptă. Tratamentul cu sulfasalazină a fost inițiat și artralgia s-a îmbunătățit. Acest caz subliniază posibilitatea dezvoltării Ac anti CCP în cadrul infecțiilor respiratorii la pacienții cu sindromul Sjogren.

Correspondence to: Taro Horino, MD, PhD, Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan
Tel: +81-88-880-2343; fax: +81-88-880-2344
Email: horinott@yahoo.co.jp

Conflict of interest disclosure: The authors declare that there are no conflicts of interest.

REFERENCES

- VITALI C., BOMBARDIERI S., JONSSON R., MOUTSOPOULOS HM., ALEXANDER EL., CARSONS SE., *et al.* Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis.* 2002;**61**(6):554–8.
- ALANI H., HENTY JR., THOMPSON NL., JURY E., CIURTIN C. Systematic review and meta-analysis of the epidemiology of polyautoimmunity in Sjögren's syndrome (secondary Sjögren's syndrome) focusing on autoimmune rheumatic diseases. *Scand J Rheumatol.* 2018;**47**(2):141–54.
- BROWN LE., FRITS ML., IANNACCONE CK., WEINBLATT ME., SHADICK NA., LIAO KP. Clinical characteristics of RA patients with secondary SS and association with joint damage. *Rheumatology (Oxford).* 2015;**54**(5):816–20.
- KIM SM., PARK E., LEE JH., LEE SH., KIM HR. The clinical significance of anti-cyclic citrullinated peptide antibody in primary Sjögren syndrome. *Rheumatol Int.* 2012;**32**(12):3963–7.
- LEE J., KOH JH., KIM JW., SUNG YK., LEE SS., CHOE JY., *et al.* Performance of the 2016 ACR-EULAR classification criteria for primary Sjögren's syndrome in a Korean cohort. *Rheumatol Int.* 2018;**38**(9):1651–60.
- TEN BRINCK RM., VAN STEENBERGEN HW., VAN DELFT MAM., VERHEUL MK., TOES REM., TROUW LA., *et al.* The risk of individual autoantibodies, autoantibody combinations and levels for arthritis development in clinically suspect arthralgia. *Rheumatology (Oxford).* 2017;**56**(12):2145–53.
- NISHIMURA K., SUGIYAMA D., KOGATA Y., TSUJI G., NAKAZAWA T., KAWANO S., *et al.* Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med.* 2007;**146**(11):797–808.
- PERRY E., KELLY C., EGGLETON P., DE SOYZA A., HUTCHINSON D. The lung in ACPA-positive rheumatoid arthritis: an initiating site of injury? *Rheumatology (Oxford).* 2014;**53**(11):1940–50.
- LAPPIN DF., APATZIDOU D., QUIRKE AM., OLIVER-BELL J., BUTCHER JP., KINANE DF., *et al.* Influence of periodontal disease, *Porphyromonas gingivalis* and cigarette smoking on systemic anti-citrullinated peptide antibody titres. *J Clin Periodontol.* 2013;**40**(10):907–15.
- MARESZ KJ., HELLVARD A., SROKA A., ADAMOWICZ K., BIELECKA E., KOZIEL J., *et al.* *Porphyromonas gingivalis* facilitates the development and progression of destructive arthritis through its unique bacterial peptidylarginine deiminase (PAD). *PLoS Pathog.* 2013;**9**(9):e1003627.
- HUTCHINSON D., SHEPSTONE L., MOOTS R., LEAR JT., LYNCH MP. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Ann Rheum Dis.* 2001;**60**(3):223–7.

12. KALLBERG H., DING B., PADYUKOV L., BENGTSSON C., RONNELID J., KLARESKOG L., *et al.* Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. *Ann Rheum Dis.* 2011;**70**(3):508–11.
13. MAKRYGIANNAKIS D., HERMANSSON M., ULFGREN AK., NICHOLAS AP., ZENDMAN AJ., EKLUND A., *et al.* Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. *Ann Rheum Dis.* 2008;**67**(10):1488–92.
14. KLARESKOG L., STOLT P., LUNDBERG K., KALLBERG H., BENGTSSON C., GRUNEWALD J., *et al.* A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum.* 2006;**54**(1):38–46.
15. KLARESKOG L., RONNELID J., LUNDBERG K., PADYUKOV L., ALFREDSSON L. Immunity to citrullinated proteins in rheumatoid arthritis. *Annu Rev Immunol.* 2008;**26**:651–75.
16. RUIZ-ESQUIDE V., GOMARA MJ., PEINADO VI., GOMEZ PUERTA JA., BARBERA JA., CANETE JDE D., *et al.* Anti-citrullinated peptide antibodies in the serum of heavy smokers without rheumatoid arthritis. A differential effect of chronic obstructive pulmonary disease? *Clin Rheumatol.* 2012;**31**(7):1047–50.
17. PABST R., GEHRKE I. Is the bronchus-associated lymphoid tissue (BALT) an integral structure of the lung in normal mammals, including humans? *Am J Respir Cell Mol Biol.* 1990;**3**(2):131–5.
18. PABST R. Is BALT a major component of the human lung immune system? *Immunol Today.* 1992;**13**(4):119–22.
19. RANGEL-MORENO J., HARTSON L., NAVARRO C., GAXIOLA M., SELMAN M., RANDALL TD. Inducible bronchus-associated lymphoid tissue (iBALT) in patients with pulmonary complications of rheumatoid arthritis. *J Clin Invest.* 2006;**116**(12):3183–94.
20. BAKA Z., GYORGY B., GEHER P., BUZAS EI., FALUS A., NAGY G. Citrullination under physiological and pathological conditions. *Joint Bone Spine.* 2012;**79**(5):431–6.
21. KAWAHITO Y., ICHINOSE S., SANO H., TSUBOUCHI Y., KOHNO M., YOSHIKAWA T., *et al.* *Mycoplasma fermentans* glycolipid-antigen as a pathogen of rheumatoid arthritis. *Biochem Biophys Res Commun.* 2008;**369**(2):561–6.

Received 30th September 2021