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CASE REPORT

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Early rheumatoid arthritis in a patient with Sjögren's syndrome and pulmonary nodular amyloidosis: clinical implication of early limited use of infliximab

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Abstract Infliximab, an anti-tumor necrosis factor α antibody, is among the most effective therapies for rheumatoid arthritis (RA). In this study, we report a patient with early RA of 6 months who has Sjögren's syndrome and pulmonary nodular lesions concomitantly. The patient did not respond to methotrexate (MTX, 6 mg per week) for 3 months. When introduction of infliximab therapy is considered, we need to exclude the possibility of pulmonary granulomatous infection and malignancy. With the use of computed tomography-guided percutaneous needle biopsy and subsequent histological examinations, this case was rapidly and confidently diagnosed as localized pulmonary nodular amyloidosis. Immunochemical staining showed light chain type nodular amyloidosis by a deposition of immunoglobulin κ light chains, which is a rare condition in a patient with Sjögren's syndrome. We started combination therapy of infliximab (200 mg per infusion) and MTX (6 mg per week). Because of severe systemic eruption, this therapy was stopped halfway through the third infusion of infliximab, and MTX monotherapy was continued. Despite the withdrawal of infliximab therapy, the C-reactive protein values were decreased to an undetectable level at week 14, and the disease activity score for 28 joints was 3.1 at week 22. Clinical remission has been maintained more than 14 months with MTX alone. Infliximab has been used only for patients with recalcitrant RA, because the cost of its lifelong use would be an economic burden in most cases. An optimal and affordable strategy for the treatment of early RA should be developed. Our findings may support the idea that the combination therapy of infliximab and MTX for early RA alters the course of the disease.

Key words Amyloidosis · CT-guided lung biopsy · Infliximab · Methotrexate · Rheumatoid arthritis · Sjögren's syndrome

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that targets synovial joints and often accompanies extra-articular manifestations. It is reported that irreversible joint damage occurs very early in the disease, and by 2 years approximately 60% of patients will show some radiographic evidence of erosion.[1] An early use of effective disease-modifying antirheumatic drugs (DMARDs) is recommended, preferably before the first radiographic changes are evident.[2] Methotrexate (MTX), among the first-line traditional DMARD with proven efficacy on radiographic progression in RA, is effective over long periods and has a better toxicity profile when compared with other DMARDs.[3] With advances in the understanding of disease pathogenesis on a molecular basis, it has been recognized that several inflammatory cytokines, in particular tumor necrosis factor α (TNFα), play critical and potential roles in rheumatoid synovitis. Biological agents counteracting TNFα activity have been shown to rapidly reduce disease activity and prevent or slow joint destruction in RA patients. Infliximab is a chimeric anti-TNFα monoclonal antibody consisting of the human constant and mouse variable regions. Since its approval by the United States Food and Drug Administration (FDA) in 1999, this agent (in combination with MTX) has been administered to a great many

patients with moderately to severely active RA refractory to MTX monotherapy.[4,5]

TNFα is not only a chief mediator of inflammation but also an integral component to healthy immune responses against infection and malignancy; therefore the use of anti-TNFα agents is anticipated to lead to an increased risk of opportunistic infections.[6–8] Postmarketing surveillance data from the FDA have identified a variety of infections occurring in patients treated with anti-TNFα agents.[9] Of particular concern are intracellular organism infections such as tuberculosis and other granulomatous infections.[6,7] Prior to the introduction of therapy with anti-TNF-α agents, patients should be rigorously screened for tuberculosis and other infections. To minimize the risk of acquiring or reactivating infectious agents, patients who have received infliximab therapy should be closely followed for signs and symptoms of infections. Furthermore, it is well known that even before the introduction of anti-TNFα agents, RA patients have a higher risk of infections than non-RA individuals.[10]

Here, we present a case of early RA in a patient who has Sjögren's syndrome and pulmonary nodular lesions. Using computed tomography (CT)-guided percutaneous needle biopsy, we made a diagnosis of pulmonary amyloidosis resulting from a deposition of immunoglobulin κ light chains. The patient showed a rapid suppression of RA activity with limited use of infliximab and she maintained clinical remission after the infliximab was discontinued. We discuss a differentiation of pulmonary nodular lesions and evaluate a sustained therapeutic benefit after the withdrawal of infliximab in early RA.

Case report

A 50-year-old woman, whose symptoms had been diagnosed as Sjögren's syndrome, was referred to our hospital for the management of sicca symptoms such as dry mouth and eyes. The diagnosis of Sjögren's syndrome was made on the basis of the following findings: dry eyes every day for more than 3 months, daily feeling of dry mouth for more than 3 months, positive Schirmer's test (less than 5 mm in 5 min), 1 focus of lymphocyte infiltrates per 4 mm^2 in a lip biopsy (a focus score 1), a positive Saxon's test (1.8 g in 2 min), and the presence of autoantibodies (anti-Ro/SS-A Ab, 146 Index; anti-La/SS-B Ab, 129 Index; antinuclear antibody, 1:80; and rheumatoid factor, 75 IU/ml). Thus, her disease fulfilled five criteria listed in the international classification criteria for Sjögren's syndrome revised by the American–European Consensus Group.[11] The patient had suffered from pain and swelling of the following joints for two months: one metacarpophalangeal joint in the left hand, three proximal interphalangeal joints in the right hand, and both wrist joints. She also complained of morning stiffness in and around these joints lasting longer than 1 h. Serum IgM rheumatoid factor was positive (75 IU/ml). Plain radiographs of hands showed evidence of bone erosions and joint space narrowing (Fig. 1). These findings met six criteria out of seven listed in the 1987 American College of Rheumatology (ACR) criteria for RA diagnosis. Besides, magnetic resonance imaging of the hand showed evidence of synovitis and bony changes. We therefore classified the patient as having early RA. Laboratory findings showed an increased C-reactive protein (CRP) level (0.92 mg/dl). The patient was also positive for anti-cyclic citrullinated peptide antibody (anti-CCP Ab, 75 IU/ml). Serum matrix metalloproteinase-3 (MMP-3), a parameter of synovial inflammation, was markedly increased (1800 ng/ml). The values of serum immunoglobulins G, M, and A were slightly elevated to 2360 mg/dl, 160 mg/dl, and 460 mg/dl, respectively, and a serum monoclonal component (M protein) was not detected. Serum soluble interleukin-2 receptor was increased (1120 pg/ml). Whole-body 67-gallium citrate scintigraphy showed significant uptakes in multiple joints and bilateral parotid glands, but there were no clinical findings suggestive of malignant lymphoma. On the basis of a diagnosis of early RA, we

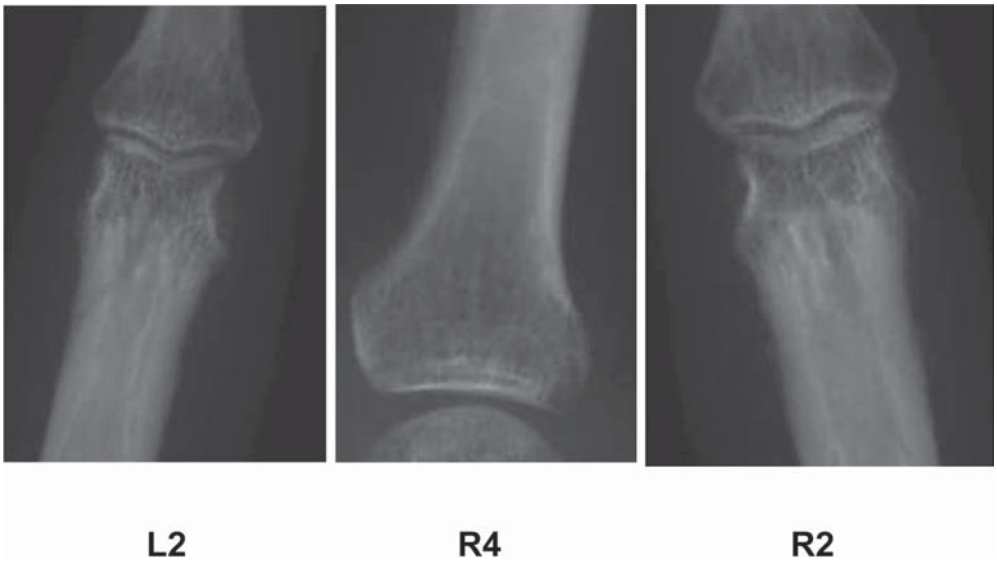

Fig. 1. Hand radiographs at the first examination. Plain radiographs of the proximal interphalangeal (PIP) joint of the index finger of the left hand (*L2*) and the metacarpophalangeal joint of the fourth finger (*R4*) and the PIP joint of the index finger (*R2*) of the right hand are shown

recommended that the patient receive methotrexate (MTX) therapy, but she rejected this proposal. Intramuscular gold treatment was started in another clinic of orthopedic surgery. Three months later, MTX (4 mg/week) was introduced to this patient.

One month after the start of MTX therapy, the patient again visited our hospital. Her clinical symptoms were exacerbated and the CRP level was markedly increased to 9.9 mg/dl. The disease activity score for 28 joints-erythrocyte sedimentation rate (DAS28-ESR) was 7.4. We increased the dosage of MTX to 6 mg/week, but she had not responded to the increased dosage of MTX for 3 months. Prednisolone was not used in conjunction with MTX because of the patient's strong refusal. Besides, her disease was erosive and rapidly advancing. To prevent further radiographic damages, we decided on the use of infliximab. Prior to the introduction of infliximab therapy, a possibility of pulmonary infection was examined. A chest X-ray film showed a nodular lesion in the lower lobe of the left lung (Fig. 2), and high-resolution CT indicated multiple nodular shadows 7–13 mm in diameter in the upper lobe of the right lung and the lower lobe of the left lung (Fig. 3). The nodular lesions were characterized by partial calcification and irregular margins. Because a tuberculin test was slightly positive (10.1×5 mm after 48 h), isoniazid (300 mg/day) was administered as a prophylaxis against tuberculosis. For histological examinations of the nodular lesions, we performed a CT-guided percutaneous needle biopsy. Low-magnification photomicrography showed eosinophilic amorphous material deposits (Fig. 4). These deposits were positive for Congo red staining and showed an apple-green color with birefringence (data not shown). By immunohistochemical testing, the amorphous material deposits stained with anti-immunoglobulin κ light chain antibody, but not with anti-λ light chain or anti-serum amyloid A (AA) protein antibody. Infiltrating lymphocytes and plasma cells, which surrounded the deposits, were stained with both anti-κ and anti-λ light chain antibodies (data not shown). No deposition of amyloid proteins was detected in biopsies of the duodenum or lip. We made a diagnosis of localized pulmonary nodular amyloidosis resulting from the deposition of immunoglobulin κ light chains.

After excluding the possibility of preexisting pulmonary infection and malignancy, we initiated infliximab therapy in combination with 6 mg/week MTX. As shown in Fig. 5, the patient responded to the first and second infusions of infliximab (200 mg per infusion). At week 6, the DAS28-ESR and the CRP value decreased to 5.4 and 4.3 mg/dl, respectively. When the patient received 40 mg of infliximab at a third infusion, a severe systemic eruption appeared. We stopped infliximab therapy, and MTX monotherapy (6 mg/week) was continued. Despite the discontinuation of infliximab therapy, the CRP value decreased to an undetectable level at week 14, and DAS28-ESR achieved 3.1 at week 22. A suppression of disease activity was maintained by the MTX monotherapy for 14 months. At week 78, the DAS28-ESR was 2.6, and the CRP value was below a detectable level. No new erosions were observed. The patient still remained in clinical remission. Repeat chest films every 2 months indicated no changes in the size of the pulmonary nodules, and the patient had no pulmonary symptoms during the course of disease.

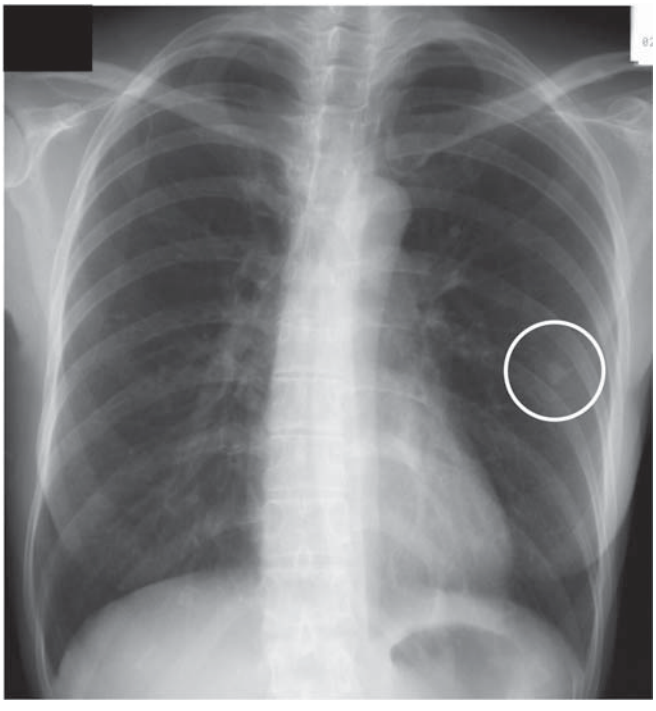

Fig. 2. Chest radiograph before the introduction of infliximab therapy. A nodular shadow is seen in the left lung (*open circle*)

Discussion

Infliximab therapy has been used mainly for long-standing and advanced RA that is resistant to conventional DMARDs. Randomized clinical trials demonstrated that infliximab therapy in combination with MTX is superior to MTX monotherapy in clinical, functional, and radiographic outcomes of active RA; however, to maintain the suppression of disease activity, lifelong treatment with infliximab has been required.[4,5] Buch et al.[12] showed a rapid flare of disease upon the withdrawal of infliximab therapy for MTX-refractory RA patients. In contrast, Quinn et al.[13] reported that early treatment with infliximab in combination with MTX for early RA significantly reduces radiographic evidence of synovitis and erosions at 1 year, and the functions and qualities of life benefits are maintained at 2 years despite a withdrawal of infliximab. Our case was early RA with 6 months of symptoms. The limited use of infliximab (a total of 440 mg) induced significant improvement of disease activity, and clinical remission has been maintained for 14 months with MTX monotherapy (Fig. 5). This result may support a hypothesis that in early RA, a "window of opportunity" exists. The combination therapy of infliximab and MTX for early RA may alter the course of disease. Currently, the high cost of anti-TNFα-agents limits their use

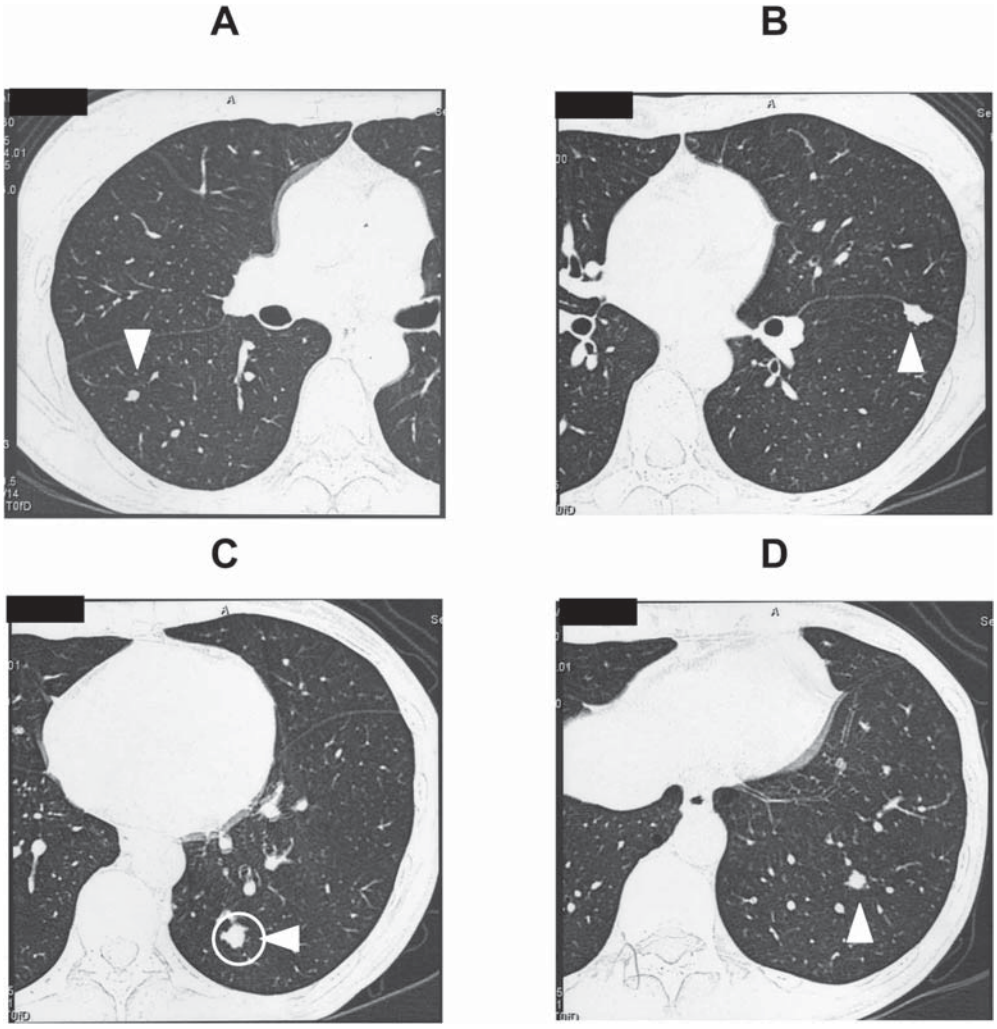

Fig. 3. The high-resolution computed tomography (CT) reveals multiple nodules with partial calcification and irregular margins (*arrowhead*). Specimens were collected from nodular lesions in the open circle by CT-guided percutaneous needle biopsy. Images at different levels are shown (**A**, lower lobe of right lung; **B–D**, lower lobe of left lung). Pulmonary amyloid deposit shown in **C** was subjected to histological examination

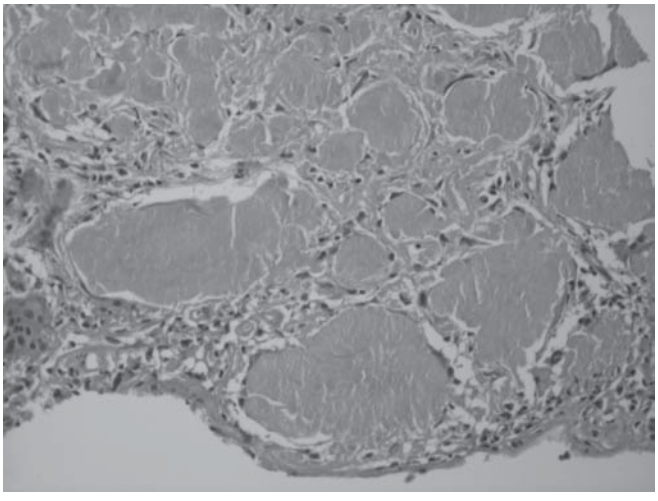

Fig. 4. Histological findings show eosinophilic amorphous material deposits surrounded by lymphocytes and plasma cells (H&E, ×100)

as first-line drugs for early RA. The present approach is to initiate treatment with a conventional DMARD and to add or substitute biological agents when DMARD therapy ended in failure. Whether this will change depends on large-scale careful surveillance of early RA. In a BeSt study for 508 patients with early RA, Goekoop-Ruiterman et al.[14,15] showed that the initial combination therapy with infliximab and MTX resulted in earlier functional improvement and less radiographic damage after 1 year and 2 years than sequential monotherapy or step-up combination therapy did. In a most recent BeSt trial, van der Kooij et al.[16] indicated that after 3 years, 64 (53%) of 120 early RA patients initially treated with infliximab and MTX successfully discontinued infliximab. Of these 64 patients, 17 (27%) remained in clinical remission after the withdrawal of all antirheumatic drugs without showing a progression of joint damage. These data support the idea that the initial combination use of infliximab and MTX for early RA can produce clinical improvements, with sustained benefits after a withdrawal of infliximab. A great opportunity to delay or prevent the disease process may be provided for early RA patients.

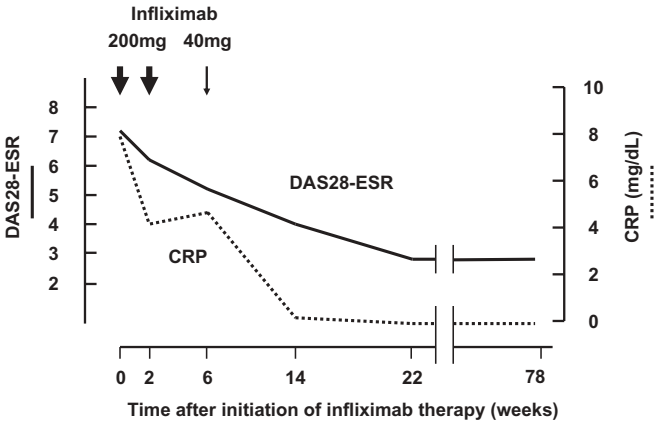

Fig. 5. Clinical course after the introduction of infliximab therapy. Patients received an intravenous infusion of infliximab (200 mg) at weeks 0, 2, and 6. Because of severe hypersensitive reaction, we failed to complete the third infusion. Only 40 mg of infliximab was infused at that time. MTX (6 mg/week) was given concomitantly. Blood samples were collected immediately prior to each infusion. The disease activity score for 28 joints-erythrocyte sedimentation rate (DAS28-ESR) was evaluated immediately before each infusion. A *thick line* and a *dotted line* show changes of the DAS28-ESR and serum C-reactive protein value, respectively

The reactivation of latent granulomatous infections has merged as a complication of infliximab therapy. Using data reported to FDA from January 1998 through September 2002, Wallis et al.[6] showed that the overall risk of granulomatous infections is 239 cases per 100 000 infliximab-treated patients. Tuberculosis was the most frequently reported disease, occurring in 144 per 100 000 who received infliximab. Granulomas represent a host defense strategy to contain intracellular microorganisms that cannot be eradicated by other cellular immune systems; therefore, the use of anti-TNFα agents theoretically induces to demolish the granuloma structures and to disseminate these infections. In Japan, the risk of new *Mycobacterium tuberculosis* infection has declined; however, because of a high risk in the past, the prevalence of latent infection may be relatively high among middle-aged and elderly individuals.[17] They remain at risk of developing active tuberculosis. Our case was slightly positive for a tuberculosis test and radiographically showed multiple nodular shadows with partial calcification in the lung (Figs. 2, 3). We therefore needed careful evaluation of a presence of latent infection before drug initiation. A differential diagnosis of pulmonary nodules in RA patients can be difficult because there are no typical radiographic findings to distinguish between granulomatous infections and the other possible causes, including malignancy, rheumatoid nodules, and other inflammatory diseases. Percutaneous needle biopsy under CT guidance has been recognized as a safe and accurate technique for establishing a diagnosis of pulmonary nodules. Using this procedure, we obtained histological and immunohistochemical findings that are characteristic of pulmonary amyloidosis with a deposition of immunoglobulin κ light chains (Fig. 4). Bleeding complications after biopsy were not observed. Therapeutic strategies for RA vary, depending on whether a diagnosis of pulmonary nodules is malignancy, benign tumor, or infection. When pulmonary nodular lesions are detected in RA patients, the CT-guided lung biopsy should be considered with the aid of radiologists.

There is a theoretical concern for an increased risk of malignancies in patients receiving infliximab therapy because the immune system plays an important role in cancer surveillance. Following the approval of infliximab, the FDA's postmarketing spontaneous adverse event reporting system (MedWatch) received reports of lymphoma in infliximab-treated patients; however, a link between the use of infliximab and the development of lymphoma remained unclear.[18] In a cohort study pooling three large databases, Setoguchi et al.[19] indicated that RA patients who received the therapy with anti-TNFα agents are unlikely to have a greater risk of developing lymphoproliferative disorders when compared with MTX-treated patients. Nevertheless, we should carefully examine a need of infliximab therapy, because population-based, case control studies have shown an increased risk of lymphoma in RA patients, especially in cases showing severe disease activity.[20] Furthermore, our case had Sjögren's syndrome, which is known to have a higher risk of developing lymphoma when compared with population-based normal controls.[21] Who should be treated with anti-TNFα agents? Most recently, Smolen et al. demonstrated that high CRP, high ESR, or persistent disease activity is associated with greater radiographic progression in early RA patients taking MTX alone, although little progression of joint damage is observed in patients receiving infliximab therapy, regardless of the abnormal levels of these parameters.[22] In our case, such predictive factors for the progression of joint damage were markedly elevated, and even during the MTX monotherapy, her disease activity was advancing. Furthermore, the patient showed erosive changes on the hand radiographs at the first visit (Fig. 1). MMP-3, a synovial-derived marker of inflammation, was markedly increased. To prevent further destructive process, we made a decision on the introduction of infliximab therapy.

Amyloidosis results from a deposition of insoluble fibrous amyloid proteins, mainly in the extracellular spaces of organs and tissues. The deposition of amyloid proteins can be limited to isolated organs without evidence of systemic involvement (localized or organ-limited amyloidosis), or it may involve every organ system of the body (systemic amyloidosis). In this study, the patient presented with multiple amyloid nodules in both lung fields (Fig. 3). We performed biopsies of the duodenum and lip; however, there was no evidence to suggest that a systemic deposition of amyloid proteins may occur. Besides, monoclonal immunoglobulins were not observed in the serum. Proteinuria, often the first symptom associated with a systemic amyloidosis, was absent in this case. Localized pulmonary nodular amyloidosis reportedly has a good prognosis.[23] Recently, the classification of amyloidosis has been based on the biochemical nature of amyloid proteins. Light chain amyloidosis (AL-type amyloidosis) is the result of fibril formation by immunoglobulin light chains in primary (idiopathic) amyloidosis and in some cases of multiple myeloma.[24] AL fibrils

are usually deposited systemically, but localized depositions of this type of amyloid protein are occasionally observed in the lung and skin.[24] It has been reported that most cases of localized pulmonary amyloidosis are classified as the AL type.[25,26] In our case, the amyloid material in pulmonary nodular lesions stained with anti-immunoglobulin κ light chain antibody. Because M protein in serum was not detected, we excluded the possibility of multiple myeloma. AL-type amyloidosis is well documented to be a plasma cell dyscrasia with a monoclonal population of plasma cells and excess light chain production in the bone marrow. However, Miyamoto et al.[27] showed that unlike systemic amyloidosis, localized AL-type pulmonary nodular amyloidosis involves the local accumulation of monoclonal plasma cells and their secreted products; therefore, they claimed that this type is a separate entity in amyloidosis. Similar findings have been shown in localized cutaneous nodular amyloidosis and nervous system nodular amyloid lesions.[28,29] Here, we failed to show an occurrence of the monoclonal expansion of plasma cells at the local sites. Infiltrating plasma cells in the vicinity of amyloid deposits stained with both anti-κ and anti-λ light chain antibodies.

Sjögren's syndrome is a chronic, slowly progressive autoimmune disease that is characterized by lymphocyte infiltration of exocrine glands and B lymphocyte hyperreactivity. Although pulmonary complications of Sjögren's syndrome have been well recognized in recent years, pulmonary nodular amyloidosis is a rare condition in patients with this syndrome.[30] Only a few reports are available, and most cases have been reported to present as multiple nodules and thin-walled cysts on the lung field.[31,32] Therefore, localized pulmonary amyloidosis should be included in the differential diagnosis for patients with Sjögren's syndrome and multiple pulmonary nodules. When lung nodules are present on chest radiographs in patients with Sjögren's syndrome, lymphoma is always suspected.[30] Our case presented with no clinical finding that raises a suspicion of lymphoma, such as lymphadenopathy, lymphopenia, splenomegaly, or cryoglobulinemia. The differential diagnosis was confidently made by using a CT-guided percutaneous lung biopsy with subsequent histological examinations. However, the monotypic staining of amyloid deposits with anti-κ light chain antibody suggests a development of monoclonal B cell population. The longitudinal monitoring of laboratory parameters and clinical symptoms associated with lymphoma is therefore appropriate for a patient with Sjögren's syndrome and AL-type amyloidosis.

In conclusion, we showed a case of early RA that had Sjögren's syndrome and AL-type localized pulmonary nodular amyloidosis concomitantly. The CT-guided percutaneous lung biopsy was a great help in excluding a possibility of pulmonary granulomatous infection, lymphoma, or other malignancies. The combined use of infliximab and MTX for early RA induced a significant improvement of disease activity, and the clinical remission has been sustained for more than 14 months despite the withdrawal of infliximab. These findings may suggest the potential for infliximab to suppress the disease activity in the limited (affordable) use for early RA.

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