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Case Report

A Case of Primary Bone Marrow Diffuse Large B-cell Lymphoma Presenting with Polyarthritis

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Polyarthritis is a common manifestation of rheumatologic disorders; however, paraneoplastic arthropathies also arise as polyarthritis or polymyalgia, particularly in patients with myelomas, lymphomas, acute leukemia, and solid tumors. Because paraneoplastic syndromes, in some instances, might be manifested before a cancer diagnosis, they are difficult to diagnose and are often misdiagnosed. We experienced a 63-year-old female patient who had nonspecific arthritis on both hands and feet accompanied by fever. She had been diagnosed as rheumatoid arthritis and treated with prednisolone and disease modifying anti-rheumatic drugs (DMARDs) including methotrexate and anti-tumor necrosis factor agents. Her arthritis did not respond with anti-rheumatic treatment and diffuse large B-cell lymphoma was diagnosed by bone marrow biopsy. After 6 cycles of chemotherapy, her arthritis was improved as well as underlying lymphoma. **(J Rheum Dis 2016;23:256-260)**

Key Words. Paraneoplastic syndromes, Diffuse large-cell lymphoma, Rheumatoid arthritis

INTRODUCTION

Polyarticular joint pain poses a diagnostic challenge because of the extensive differential diagnosis. Polyarthritis which affects 5 or more joints is a common manifestation of rheumatic diseases characterized with inflammatory arthritis such as rheumatoid arthritis (RA) and spondyloarthropathy. However, it can be occurred in other diseases such as crystal-induced arthritis, viral infections, or malignant tumor [1]. By thorough history and a complete physical examination, rheumatologists need to keep the diagnosis open in evaluating patients who present with pain in multiple joints.

Application of recently developed 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA provided an opportunity to identify and treat those patients with early inflammatory arthritis who progress to future RA. The new 2010 criteria is a diagnostic tool with higher sensitivity and specificity compared to previous ACR 1987 criteria. The new criteria are markedly more effective at detecting RA early on than were the former 1987 criteria. However, it is unless they are employed judiciously, many patients will be inappropriately labeled as having RA and subjected to treatments they don't actually [2].

Paraneoplastic rheumatic disorders, one of categories of differential diagnosis from RA, are defined as rheumatic symptoms resulting from an underlying malignant disease, which is not directly related to a tumor or metastasis [3]. In Korea, there have been a few cases of paraneoplastic syndrome appearing as a form of arthritis reported and most of them are solid tumors such as ovarian cancer, pancreatic cancer, and metastatic adenocarcinoma of unknown primary site [4-6]. However, hematologic malignancy as an underlying disease is rarely reported.

Here we report a patient presenting with polyarthritis who was initially diagnosed as RA with satisfying 2010

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criteria but treated unsuccessfully with disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) and anti-tumor necrosis factor (TNF) agents. She was finally diagnosed with diffuse large B-cell lymphoma limited to the bone marrow and improved of arthritis with chemotherapy.

CASE REPORT

A 63-year-old woman visited our clinic with a complaint of symmetrical polyarthritis in the hands, wrists and feet.

History of present illness

Arthralgia first occurred in both hands, wrists, and knees at 4 months before first visit to our hospital. Initially, she had a mild fever, and treated by antibiotics according to pyelonephritis. She had visited other referral university hospital and had been seen with a rheumatologist. After performing full examinations including laboratory tests and imaging studies, she had been diagnosed as seronegative RA. She had been treated with conventional DMARDs at least 3 months with combination of MTX, hydroxychloroquine, sulfasalazine, or leflunomide. Since there was no improvement in her symptoms, combination therapy with MTX and etanercept was started. During use of DMARDs, sensorineural hearing loss was suddenly developed and high dose steroid treatment was added. Although DMARDs treatment was not showing satisfactory response, high dose steroid was effective for controlling her arthritis. When prednisolone dose was reduced to 15 mg daily; however, the arthritis deteriorated again. Her personal and family history was not specific.

Physical examination

Upon admission, the patient had a fever of 38.2°C, while her other vital signs were stable: heart rate, 90 beats/min; breathing rate, 20 breaths/min; and blood pressure, 120/70 mmHg. The fever occurred mostly in the night time and was accompanied by the systemic symptom of cold sweat. However, there were no other subjective symptoms and no observable weight loss or lymphadenopathy. Tests of the musculoskeletal system displayed edema and tenderness in the metacarpophalanges (MCP), proximal interphalanges (PIP), and distal interphalanges (DIP) of all fingers and toes as well as other joints of shoulders, wrists, knees, and ankles (Figure 1A). One unusual finding was that the patient complained of more pain when pressure was applied to the tendon proximal to the joints than when the joints themselves were pressed.

Laboratory test findings

In peripheral blood testing, the leukocyte count was 4,200/mm^3, hemoglobin level was 9.8 g/dL, and platelet count was 558,000/mm^3, while no abnormal cells were observed in the initial test. But after a week, immature

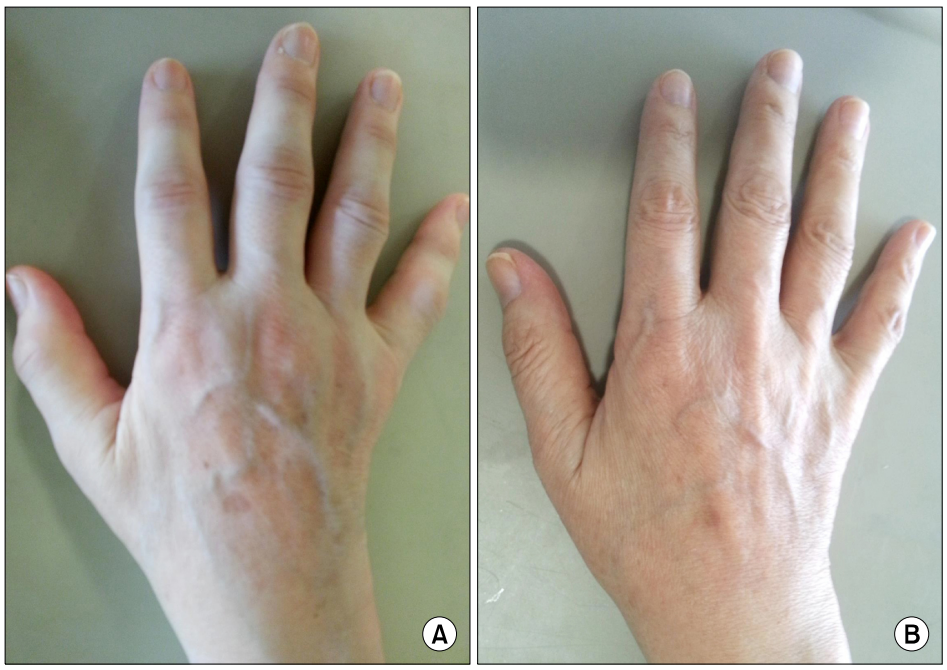

Figure 1. Photographs of right hand showing polyarthritis at first visit (A) and improved arthritis after 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy (B).

myeloblasts account for nearly 2 percent are seen in peripheral blood testing. Biochemical test results were in the normal ranges at 21 U/L for aspartate aminotransferase, 38 U/L for alanine aminotransferase, 16.2 mg/dL for blood urea nitrogen, 0.8 mg/dL for creatinine, and 77 mL/min/1.73 m^2 for the estimated glomerular filtration rate. Serum tests were negative for both rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody, and the C-reactive protein (CRP) level and the erythrocyte sedimentation rate (ESR) were elevated at 6.0 mg/dL and 63 mm/h, respectively. Perinuclear skeleton type (1:80) was detected in an antinuclear antibody test, and no bacteria was found in blood and urine culture tests performed to investigate the fever.

Diagnostic imaging

On simple radiography of the joints, soft tissue edema was observed around the knees and the PIP joints of both hands, and periarticular osteoporosis was observed, but no obvious erosion was seen. However, on magnetic resonance imaging (MRI) of the right hand, multiple erosions were observed in the MCP joints and the wrist and synovitis and edema were observed around the PIP and DIP. These findings are similar to those of RA (Figure 2A). On whole body bone scan, a symmetrical increased uptake was observed in the MCP, PIP and DIP joints on both hands (Figure 3). Symmetrical involvement of hands and feet was common manifestation of early RA, especially obvious inflammation of PIP joints of the fingers.

Diagnosis of lymphoma

Although the diagnostic imaging results were relatively consistent with RA, paraneoplastic syndrome from hematologic malignancy was strongly suspected because of

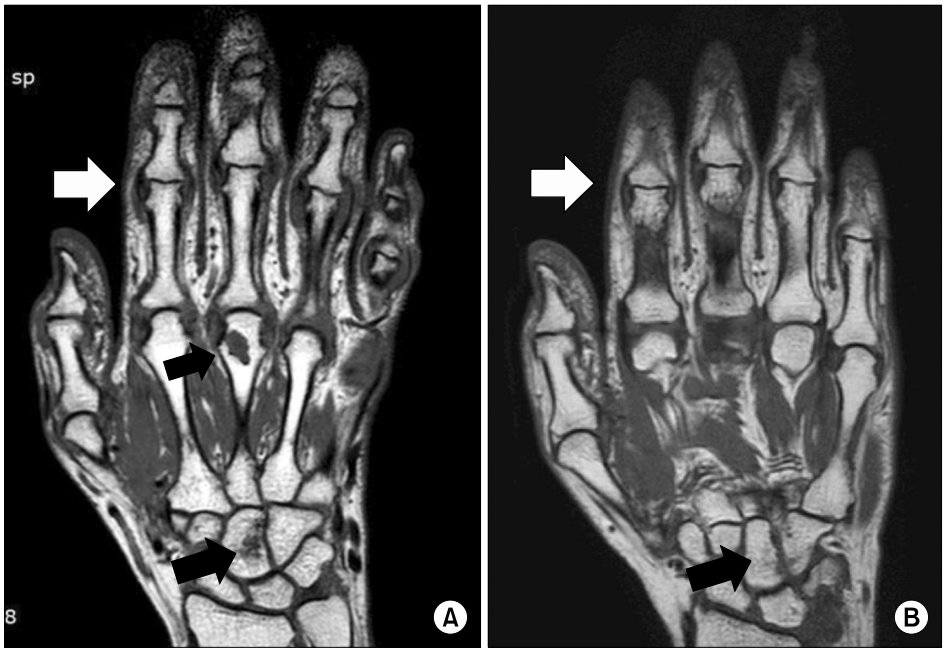

Figure 2. T1-weighted magnetic resonance imaging of right hand at first visit (A) and after 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy (B). Tenosynovitis of proximal interphalanges joints (white arrows) and bone erosions at carpal bones (black arrows) and metacarpophalanges joints (A) had been resolved after 6 cycles of R-CHOP chemotherapy (B).

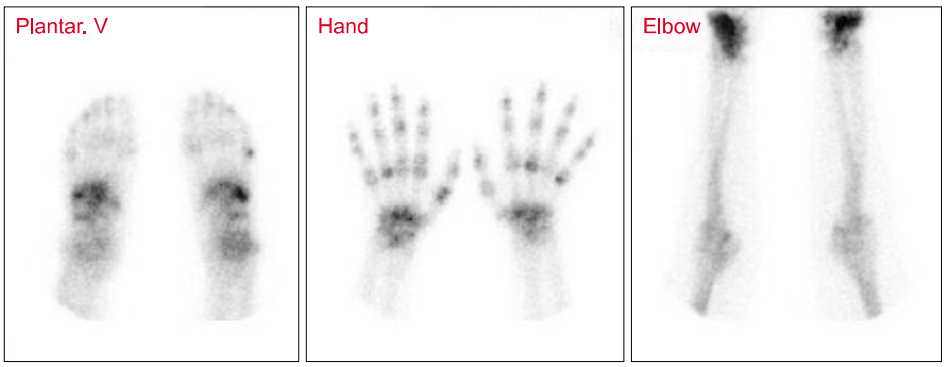

Figure 3. Whole body bone scintigraphy at first visit. Both wrists, proximal interphalanges, distal interphalanges, and metacarpophalanges joints on hands showed increased symmetric uptake and tarsometatarsal joints and metatarsophalangeal joins were also showed increased uptake.

immature myeloblasts seen in peripheral blood testing, night-time fever and cold sweat like B symptoms. Therefore, a bone marrow biopsy was conducted to identify the hematologic disorder. On the bone marrow biopsy, there was a dense group of lymphocytes with diverse appearances in hematoxylin and eosin stain with 400 magnification (Figure 4), and immunohistochemical staining showed that the biopsy sample was positive for CD79a, CD20, and BCL-2, finally, the patient was diagnosed with diffuse large B-cell lymphoma. A whole-body positron emission tomography computed tomography revealed findings seen in lymphoma, including increased uptake of bone marrow, and spleen and increased size of axillary lymph node.

Treatment and clinical progress

Intravenous methylprednisolone (62.5 mg/d) was applied on the first day of hospitalization. Antipyretics were not used, but fever detected until third day and then subsided. During hospitalization, steroid was administered without any DMARD or biologic agents. For anticancer drugs, rituximab, cyclophosphamide, doxorubicin, and vincristine (R-CHOP) was initiated, and prednisolone (100 mg/d) was administered. Steroid dose was gradually reduced: prednisolone (15 mg/d) was used during the sixth and final anti-cancer treatment.

During chemotherapy, the patient's arthralgia and edema were resolved (Figure 1B). As 10 months later from remission arthralgia, follow-up MRI of the hands revealed that the previously observed edema in the PIP joints and erosions in MCP joints were disappeared (Figure 2B). As follow-up bone marrow biopsy revealed no further findings of lymphoma, the prednisolone dose was reduced by half every 3 months, and has been stopped since. The patient has been followed up as an outpatient of hematology and rheumatology department; she has not shown any recurrence of the arthritis and bone erosion in X-ray. She maintained seroconversion of ESR, CRP, negative finding of RF and anti-CCP antibodies for approximately 1 year since stopping steroid and DMARDs.

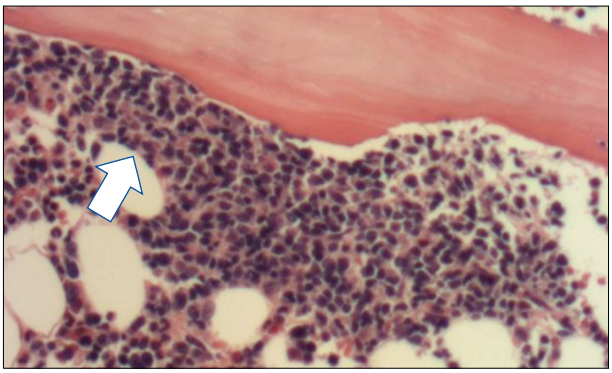

Figure 4. Bone marrow biopsy showed multiple lymphocytes concentrated with the various features. Lymphoid cells are oval shape and high nucleus-cytoplasm ratio (H&E, ×400; white arrow).

DISCUSSION

RA causes inflammation in the joint areas resulting in arthralgia and swelling characterized by morning stiffness that lasts less than one hour. It mostly occurs symmetrically, and the main sites of invasion are the PIP, MCP, wrist, knee, and elbow joints. Although systemic fever is rare, high activity can cause a slight fever that is sometimes accompanied by symptoms like fatigue and pantalgia.

The above-mentioned case had features similar to those of RA including symmetrical polyarthritis and invasion of the PIP, MCP, and knee joints. When the 2010 criteria for RA diagnosis was applied to the present case, RA could be diagnosed in cases of invasions in >10 small joints, negative RF and anti-CCP antibodies, elevated inflammatory markers, and a duration of more than six weeks, corresponding to a total of seven points [7]. Therefore, an initial diagnosis of RA by a rheumatologist was inevitable.

However, there was a no response to various DMARDs or anti-TNF agents, the patient was only responsive to steroids; this matter requires different diagnosis. In other words, if a patient is viewed only in terms of the RA classification criteria, the possibility polyarthritis caused by other underlying diseases could be underestimated. The findings in the present case of multiple involvements of the DIP joints accompanied by systemic symptoms such as intermittent night time fever were not typical symptoms of RA. These findings suggest that the risk of accompanied paraneoplastic syndrome is higher than that of RA.

A paraneoplastic syndrome is symptoms that are the consequences of cancer in the body but that unlike mass effect is not due to the local presence of cancer cells. These phenomena are mediated by humoral factors by hormones or cytokines excreted by tumor cells or by an immune response against the tumor. Typical features of paraneoplastic rheumatic syndrome are asymmetrical arthritis, negative finding of RF, elderly patients aged less

than 50 years, and systemic symptoms such as fever, weight loss, and night sweat. But various symptoms are appeared in paraneoplastic rheumatic syndrome, especially symmetric arthralgia mimics RA in other study and cases [5,8].

As patients with rheumatic disease have a higher incidence of certain malignant lymphoma compared to healthy people, it is necessary to check whether rheumatic disease is involved, even when paraneoplastic syndrome is suspected. In particular, lymphoma is known to occur twice as frequently in patients with RA than in typical individuals [9], as shown in a study of patients who had RA for several years; lymphoma is known to be caused when accompanied by Epstein-Barr virus and when immunosuppressed agents such as azathioprine, MTX, and TNF inhibitor have been used for a long time [10,11]. For the patient in case, the duration of arthritis was not long and DMARDS had only been used for 3 months. In particular, paraneoplastic syndrome was supported by the improvement in the lymphoma, which was no longer observed in follow-up bone marrow biopsy after anti-cancer therapy. She improved of the RA–like symptoms, such as the erosions on MRI, disappearance of joint pain and edema for 1 year after stopping the steroid treatment. Also, she maintained normal range of CRP, ESR, negative finding of RF and anti-CCP antibodies. Accordingly, the possibility of concurrent development of lymphoma with RA was considered low.

In conclusion, arthritic symptoms caused by paraneoplastic syndrome worsen as tumors progress and recur, treatment for the original tumor will usually improve the arthritic symptoms. Thus, delayed diagnosis can cause rapid deterioration in prognosis, thus an accurate diagnosis is considered critical. So we should be suspected the possibility of paraneoplastic syndrome in patients who met RA criteria, but resistant typical RA medication, had systemic symptoms like fever, night sweat or weight loss.

SUMMARY

Along with a discussion of the literature, here in we report of a 63-year-old woman who was diagnosed with RA due to symmetric arthritis in the hands and feet and was treated appropriately but unsuccessfully. The patient was ultimately diagnosed with diffuse large B-cell lymphoma limited to the bone marrow with accompanying paraneoplastic syndrome.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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