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Rheumatoid Arthritis Associated with Myelodysplastic Syndrome : A Case Report

Myelodysplastic syndromes (MDS) are a group of refractory anemias resulting from a clonal stem cell disorder often associated with cytogenetic abnormalities. There is increasing recognition of immunological abnormalities in patients with MDS, including defective B- and T-cell function, hyper- or hypogammaglobulinemia and monoclonal gammopathy. MDS have been associated with Sjögren's syndrome, polymyalgia rheumatica, relapsing polychondritis and systemic lupus erythematosus. Although there may be various rheumatologic features, including acute arthritis in MDS, chronic inflammatory arthritis is uncommonly combined. There have been a few reports that described cases of rheumatoid arthritis (RA) concurrent with MDS, but advanced rheumatoid arthritis with typical joint deformities has rarely been reported. We report a case of rheumatoid arthritis with atlantoaxial subluxation combined with refractory anemia in a 31-year-old woman.

Key Words: *Myelodysplastic syndromes, Rheumatoid arthritis*

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of refractory anemias resulting from a clonal stem cell disorder often associated with cytogenetic abnormalities (1). There is increasing recognition of immunological abnormalities in patients with MDS, including both cellular and humoral immunities which were generally ascribed to immune dysregulation and/or clonal involvement of lymphocytic cell line (2-4). Various rheumatic manifestations, ranging from cutaneous vasculitis and acute arthritis to classic connective tissue disorders such as Sjögren's syndrome, polymyalgia rheumatica and relapsing polychondritis, have been described in patients with MDS (5-7). Chronic inflammatory arthritis, including several cases of rheumatoid arthritis, has been reported to be associated with MDS (7, 8). But advanced rheumatoid arthritis with typical joint deformities has rarely been reported. We describe a case of rheumatoid arthritis with atlantoaxial subluxation which has been combined with refractory anemia.

CASE REPORT

A 31-year-old female was admitted to our hospital on November 1997 with nine years' history of pain and swelling of multiple joints. In 1985, the patient was diagnosed as refractory anemia, and treated with androgen, low-dose glucocorticoid, pyridoxine, and intermittent transfusions. Since 1989, she had experienced morning stiffness persisting for more than one hour and pain and swelling of small joints of hands and feet, wrists, elbows, knees and ankles. Rheumatoid factor was positive. She had been diagnosed as rheumatoid arthritis but had taken medications for arthritis irregularly. On admission, she complained of painful swelling and deformities of multiple joints.

On physical examination, blood pressure was 120/80 mmHg, pulse rate 85/min and body temperature 36.6℃. She had a cushingoid appearance with purple striae on abdomen, hyperpigmented skin and pale conjunctivae. Joint examination revealed swelling and warmth on multiple joints, boutonniere deformities of the right fingers, subluxation of both metacarpophalangeal joints, limitation of motion of both wrists, flexion contractures and varus deformities of both knees and valgus deformities of both halluces.

Laboratory examination showed that hemoglobin was 5.5 g/dL, hematocrit 15.8%, MCV 102.7 fL, reticulocyte 0.3%, white blood cell 1,840/μL, platelet 13,000/μL, total protein 6.5 g/dL, albumin 3.9 g/dL, AST 571 U/L,

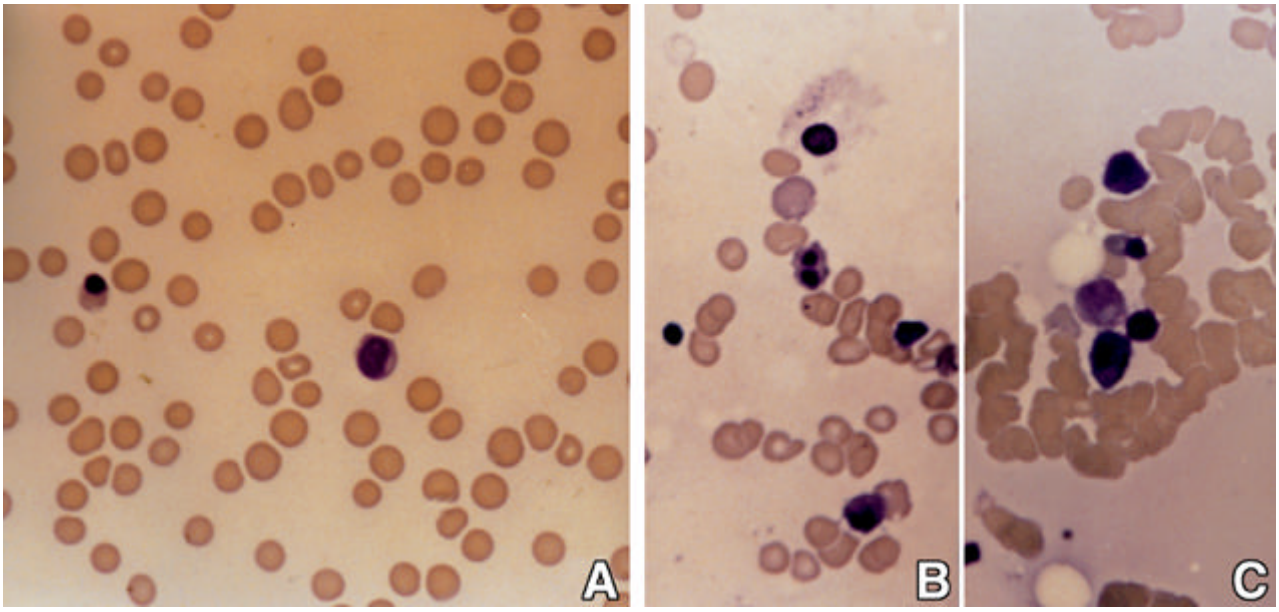

Fig. 1. Peripheral blood film shows pancytopenia with anisocytosis, poikilocytosis and abnormal nucleated cells (A: Wright stain, ×200). Bone marrow shows dyserythropoiesis (B & C: Wright stain, ×200).

ALT 1,021 U/L, ALP 2,221 U/L, and alpha-fetoprotein 3.7 ng/mL. Bone marrow biopsy revealed hypocellularity with erythroid hyperplasia and dysplasia, myeloid to erythroid (M:E) ratio 0.6:1, and hypoplastic granulocytic series. Megakaryocytes were present in adequate numbers and there were no excess blasts (Fig. 1). Serum viral hepatitis marker study showed that HBs antigen was positive, HBe antigen positive, HBV DNA 869.2 pg/mL, HCV antibody (2nd generation, LG Biotec, Korea) positive and HCV RNA (RT-PCR, Sorin, Italy) positive. HIV antibody, ANA, serum vitamin B_{12} and folate levels were normal. Joint radiographs showed diffuse osteopenia especially near joints, destructed and deformed peripheral joints, and atlantoaxial subluxation (Fig. 2). Abdominal ultrasonography revealed markedly increased hepatic parenchymal echogenicity and multiple variable-sized masses in both lobes. Abdominal MRI showed nodules with high signal intensity in the liver and hemochro-

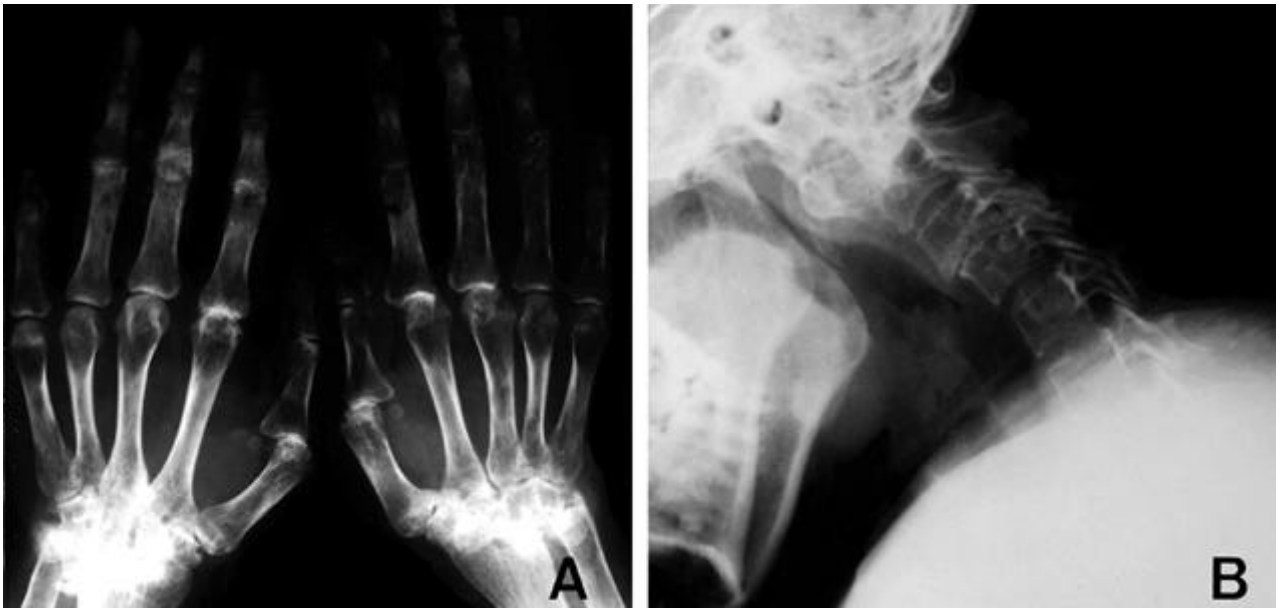

Fig. 2. Both hand radiograph demonstrates advanced arthritis with bony ankylosis (A). Flexion view of cervical spine shows marked atlantoaxial subluxation (B).

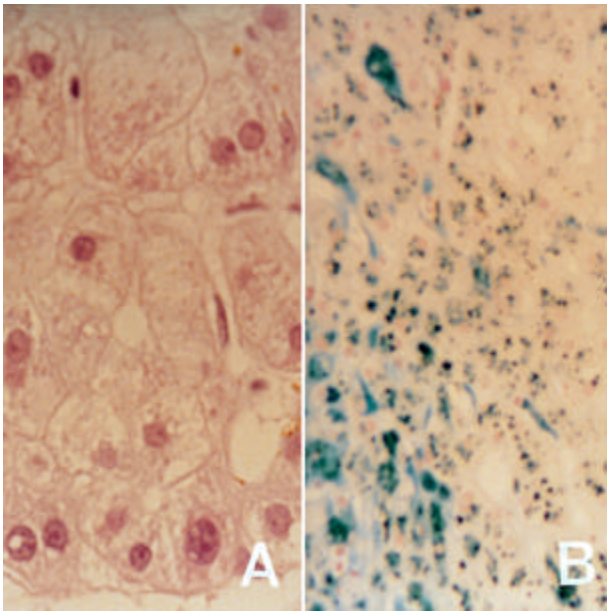

Fig. 3. Liver biopsy shows large atypical hepatocytes with pseudoglandular pattern (A: H&E stain, ×400) and massive iron deposit (B: Prussian Blue stain, ×100).

matosis of liver and spleen on T2 weighted image. Ultrasonography-guided liver biopsy revealed well-differentiated hepatocellular carcinoma and hemosiderosis (Fig. 3). The patient was diagnosed as having advanced rheumatoid arthritis with atlantoaxial subluxation combined with refractory anemia, secondary hemochromatosis and hepatocellular carcinoma. Transhepatic arterial embolization was done for hepatocellular carcinoma. Joint symptoms were treated with nonsteroidal antiinflammatory agent, hydroxychloroquine and low dose steroid, but therapeutic response was poor. Methotrexate and immunosuppressive agents could not be used because of pancytopenia, hepatic problems and hepatitis virus infection. She succumbed after five months of follow up.

DISCUSSION

MDS represent a diverse spectrum of disorders which result from the clonal expansion of bone marrow derived pleuripotential stem cells, and range from refractory anemia to a preleukemic state. Peripheral cytopenias involving one or more cell lines and a variety of dysplastic morphology and cellular dysfunctions, combined with cellular marrow were its hematological hallmarks. The frequently detectable cytogenetic abnormalities confirm the clonal nature of these disorders and a variable percentage of cases eventually progress to acute leukemia (1). There are evidences that clonal expansion occurs not only in hemopoietic cells but also in the T and B lymphocytes, which may be the mechanism of various immunologic abnormalities in MDS such as, reduced NK cell activity with decreased number of NK cells, reduced number of helper T cells, impaired function of T and B cells, and serologic abnormalities including hypergammaglobulinemia, monoclonal gammopathy, positive Coombs test and other autoantibodies (2-4).

Some reports have identified autoimmune manifestations in patients with MDS, ranging from asymptomatic serological immunological abnormalities and acute or chronic autoimmune manifestations to classic connective tissue disorders such as Sjögren's syndrome, polymyalgia rheumatica, relapsing polychondritis, systemic lupus erythematosus, rheumatoid arthritis and mixed connective tissue disease (5-8, 15).

The pathogenetic abnormalities which may cause secondary rheumatic features in MDS have not been elucidated but it is unlikely that they simply represent a coincidental occurrence. There has been a number of reports describing dysregulation of cellular and humoral immune function in MDS, and the immune abnormalities have been advocated as the causes of the rheumatic manifestations (2-4). Abnormal T-cell responses to antigen presentation and/or abnormal B-cell and T-cell interactions especially may be important in the pathogenesis of 'immune dysregulation' leading to the development of autoimmune disorders (5).

Among the various rheumatic manifestations in MDS, arthritis has been reported to occur only in a minority of patients. Although arthropathy associated with synovial hemosiderosis in sideroblastic anemia (16) and synovial infiltration of immature cells in refractory anemia with excess blasts (17) have been reported, inflammatory arthritis is the major presentation. Most of the reported cases had acute seronegative arthritis which were transient or recurrent (5, 9, 10) but chronic inflammatory arthritis has also been reported (7, 8). These arthritis may be either seronegative or seropositive and the interval between the presentation of arthritis and the diagnosis of a hematologic disorder was variable. Both were apparent within a few years, but Kuzmich et al. (7) reported two cases of rheumatoid arthritis which preceded the diagnosis of hematologic disease by three to 20 years. Most cases developed seronegative polyarthritis which responded well to steroid therapy (5, 8-10). In our case, symmetrical seropositive polyarthritis developed four years after the diagnosis of MDS and multiple transfusions. Arthropathy due to secondary hemochromatosis presents typically as absence of swelling or warmth of involved joints and usually shows degenerative changes which often involve metacarpophalangeal joints (18, 19). Although arthrocentesis was not performed because of severe thrombocytopenia, there were evidences that favor the inflammatory nature of arthritis in our case. First,

most of the involved joints were swollen and warm. Second, there were severe bony destructions with variable degree of joint deformities, and the atlantoaxial joint showed marked horizontal subluxation which is one of the characteristics of rheumatoid arthritis. In addition, she had a few rheumatoid nodules and positive rheumatoid factor. Previously reported cases showed good responses to non-steroidal antiinflammatory drugs, steroid or hydroxychloroquine, but our case showed poor response to those drugs. The reasons for poor response may be that our case had advanced rheumatoid arthritis with severe joint deformities and therapeutic regimens were limited because of pancytopenia, hepatic problems and hepatitis virus infection. We believe this to be the first case describing advanced rheumatoid arthritis combined with refractory anemia in Korea.

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