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Case Report
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Leukemic Arthritis in Acute Promyelocytic Leukemia

Wen-Chi Y[1,2,3]*

[1]Department of Internal Medicine, Division of Hematology and Medical Oncology, Pingtung Christian Hospital, Taiwan

[2]School of Medicine, College of Medicine, National Sun Yat-sen University, Taiwan

[3]College of Nursing, Meiho University, Taiwan

Abstract

Acute Promyelocytic Leukemia (APL) is a hematological malignancy with abnormal clone of translocation between chromosome 15 and 17 (t(15;17)) and appearance of *PML-RARα* fusion gene. Extramedullary involvement of APL is rare and the most common site is central nervous system. It has been reported that a rheumatoid arthritis combined with APL and shown a rare side effect of retinoid acid (ATRA) and arsenic treatment related arthritis. In our review, there is no report showed arthritis with leukemia cells infiltration in APL before. Gouty arthritis attack typically showed hyperuricemia. However, around 10% to 49% patients with gout attack had normal serum uric acid level. Monosodium urate crystals in synovial fluid is still the golden standard to diagnose of acute gout attack. Here, we report a patient with leukemic arthritis, superimposed in gouty arthritis, as the initial presentation of APL. We analysis the synovial fluid and confirmed by positive finding of *PML-RARα* fusion gene using RT-PCR.

Case Presentation

A 53-year-old male patient is a heavy smoker, alcohol abuser and had betel nut regular chewing history. He denied any underlying diseases. He suffered from arthralgia over right ankle and knee joints for few weeks and he couldn't stand. General malaise was also complained for more than 3 months. Neither fever, nor body weight loss and bleeding tendency were noted. We didn't find any abnormality, except local heat, reddish, swelling and tenderness over right knee and ankle joints, on physical examination.

Laboratory examination showed white blood count of 28,800/ul with 24% blasts and 50% promyelocytes, hemoglobulin of 4.6 g/dl, MCV of 104 fl and platelet of 127,000/ul. Other examinations were liver function: SGOT/SGPT 26/30 IU/L; renal function: BUN/Creatinine 24.3/1.14 mg/dl; C-Reactive Protein (CRP) 63.62 mg/L (normal range is less than 5 mg/L); uric acid: 2.4 mg/L, ANA <1:40, rheumatoid factor: 41.7 IU/ml (normal range <20 IU/ml) and anti-Cyclic Citrullinated Peptide antibody (anti-CCP) showed negative result. DIC profile showed fibrinogen: 475 mg/dL; fibrin degradation product: 30.2 ug/ml; D-Dimer: 9.42 mg/L without PT, PTT prolong. We performed bone marrow study for him with atypical hypocellularity picture and hypogranular promyelocytes (Figure 1). Surface marker and special stain analysis revealed HLA-DR (+): 0.7%, CD11b: 5.1%, CD13: 88.3%, CD14: 5.5%, CD33: 99.1%, CD34: 15.9% and negative for lymphoid markers; peroxidase stain was 98%; Sudan black B stain was 100%; Naphthol AS-D Chloroacetate is 100%. Cytogenetic study showed t(15;17) and molecular study revealed *PML-RARα* fusion gene in Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) (Figure 2A). Three sets of primers were used for detecting *PML-RARα* [1]. According to above data, Acute Promyelocytic Leukemia (APL) was diagnosed. Image study of right knee Computed Tomography (CT) showed fluid accumulation in both knee joints cavities, with the right site dominant. Focal soft tissue swelling was also noted (Figure 3). For right synovial fluid analysis, the color of aspiration fluid is sticky yellowish and the component contained 107,910/cumm cell count with 90% neutrophils, 2% lymphocytes, and 8% monocytes with Red Blood Cell count (RBC) of 5,940/cumm. The surface markers analysis of joint fluid showed CD11b: 99.9%, CD13: 100%, CD14: 94.6%, CD33: 99.8%, and CD34: 4.8%. *PML-RARα* fusion gene also can be detected in joint fluid (Figure 2B). On the other hands, monosodium urate crystals were also noted in polarizing microscope. However, neither bacterial nor fungus was cultured after 7 days culture.

We started to use standard treatment, All-Trans-Retinoic Acid (ATRA) 45 mg/m^2, for APL. Allopurinol and colchicine were also prescribed for gouty arthritis and preventing tumor lysis

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Correspondence:
Yang Wen-Chi, Department of Internal Medicine, Division of Hematology and Medical Oncology, Pingtung Christian Hospital, Pingtung, Taiwan, Tel: 886-8-7368686;

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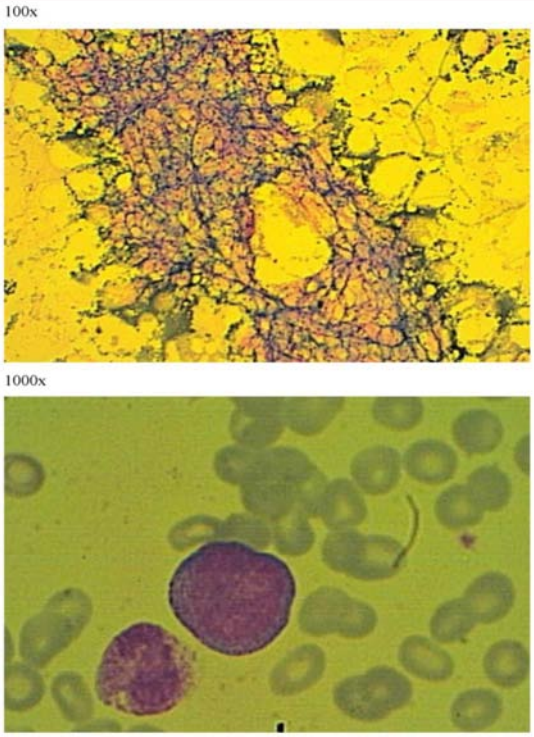

Figure 1: Bone marrow smear: Hypocellularity with decrease of megakaryocytes. The myeloid series was poor maturation with atypical hypogranulated promyelocytes. The erythroid series was hypoplasia.

syndrome. Five days later, arthritis got improved and he could walk again while the peripheral blood revealed white blood cell count 7,800 /ul with blast of 6%, and promyelocytes of 16%, hemoglobulin 7.9 g/dl and platelet 41,000/ul. Re-survey right joint fluid showed cell count of 20,800/cumm with 90% segment cells, 3% lymphocytes and 7% monocytes and RBC contain is 6400/cumm.

Discussion

Acute Promyelocytic Leukemia (APL) is a specific subtype of Acute Myeloid Leukemia (AML), comprising approximately 10% of AML [2], with character of promyelocytes dominant with or without Auer rods (typical or variant) [3], and chromosomal rearrangements of 17q21 [4], leading to fusion of the gene encoding Retinoic Acid Receptor Alpha (*RARα*) to a number of alternative partner genes (X), the most frequent of which are *PML* (>95%), *PLZF* (0.8%) and *NPM* (0.5%) [5-7]. The clinical pictures of APL are fever, anemia and bleeding diathesis, with or without thrombosis due to disseminated intravascular coagulation [8]. Extramedullary involvement of APL is rare and the most common site is central nervous system [9]. Arthritis was reported as a Rheumatoid Arthritis (RA) combined with APL [10] and a rare side effect of Retinoid Acid (ATRA) [11] and arsenic treatment [12]. Leukemic arthritis is an uncommon complication of both acute and chronic leukemias. It occurs in 12% to 65% of childhood leukemia cases and 4% to 13% of adult leukemia cases and its majority involved large joints. Involved joints usually are warm, swollen, and tender [13]. In Silverstein and Kelly's series of 450 patients with acute leukemia, the frequency of leukemic arthritis was 4% in adult [14]. However, leukemic arthritis in APL has not been reported as an initial symptom and sign in our knowledge.

To survey the cause of arthritis, we checked the serum autoimmune

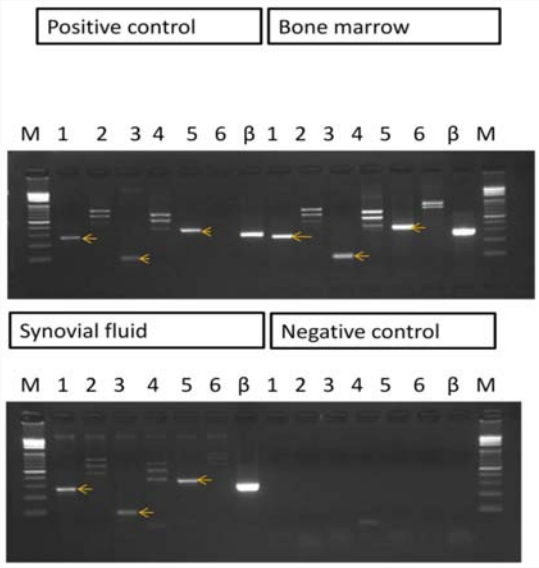

Figure 2: Reverse Transcription Polymerase Chain Reaction (RT-PCR) of PML- RARα of bone marrow and right knee joint synovial fluid. M: DNA ladder; 1,2,3,4,5,6: Primers; β: β actin

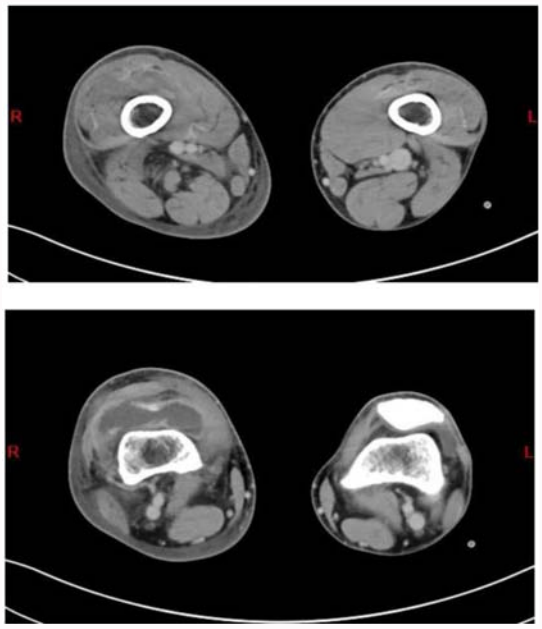

Figure 3: Computed Tomography (CT) scan of knee joints. Homogeneous fluid accumulation over right knee joint cavity. Mild fluid accumulation over left knee joint cavity. Soft tissue swelling surrounding right knee joint.

markers, including Rheumatoid Factor (FF), ANA, and serum uric acid level. We also collect right knee synovial fluid and surveyed by cell count analysis, culture for bacterial or fugal pathogens, checking by polarizing-microscope and analysis *PML-RARα* by RT-PCR with 3 sets of primers [1]. The serum Rheumatoid Factor (RF) was higher than normal, but ANA and anti-CCP showed negative result. There are 15% of rheumatoid arthritis patients couldn't detect positive RF [15] and approximately 10% of the healthy population got positive results. Anti-CCP is a marker for RA, with high specific (up to 95%) but less sensitive of detection [15]. According to the clinical symptoms of this patient, he had unilateral arthralgia over right knee and ankle

joints. Those were different to the symptoms of RA, that is normally showed symmetric arthralgia and rarely involve ankle joints. In right knee joint synovial fluid analysis, monosodium urate crystals noted in joint fluid under polarizing-microscope study that gouty arthritis was diagnosed. However, the serum uric acid level was within normal limit. Although hyperuricemia is typically occurred under gout attack, around 10% to 49% patients with acute gout attack had normal serum uric acid level [16-21]. Leukemia cells were also found in joint fluid which proven by *PML-RARα* fusion gene detection by Reverse Transcription Polymerase Chain Reaction (RT-PCR). Because the component of synovial fluid cell count, the major white blood cells were neutrophils and that is not similar to the picture of peripheral blood (blasts and promyelocytes dominant). We can rule out that was contaminate by blood. The possible reason of leukemic cells accumulation in joint space are small thrombus formation in small vein and blocks venous return which cause increasing local pressure in the lower limbs. Impeded white blood cells would penetrate to third space and cause leukemic arthritis. On the other hand, cytokine releasing, like TNF-α and IL-1β [22], may increase the permeability of vessel which lead leukemic cells leak from blood vessels [23]. Here, we report a very rare case of leukemic arthritis, superimposed in gouty arthritis, in APL patient.

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