CASE REPORT

Inflammatory Arthritis Preceded Leukemic Arthritis in a 60-Year-Old Female: A Case Report

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Background: Leukemic arthritis is an uncommon presentation of acute and chronic leukemia which might cause by local reaction to bony, periosteal, or capsular infiltration by malignant cells. The patient may present with seronegative inflammatory arthritis, which precedes the diagnosis of leukemia and is usually resistant to corticosteroid treatment.

Case Report: The authors report a case of 60-year-old woman with leukemic arthritis, who was diagnosed with acute leukemia after the initial onset of arthritis. The patient had chronic arthritis in both knees and in her left ankle with unintentional weight loss over a 3-month period. The investigations revealed high C-reactive protein, and was negative for the rheumatoid factor, anti-cyclic citrullinated peptide, HLA-B27, anti-nuclear antibody, and anti-double stranded DNA. Synovial fluid analysis showed leukocytosis but was negative for both bacterial culture and polymerase chain reaction for tuberculosis. Even though the crystals were unable to be identified in the patient's synovial fluid, the preliminary diagnosis for this patient was gouty arthritis. After systemic and intra-articular steroid injections, her symptoms did not improve even after treatment with allopurinol and colchicine. Her blood tests and a test of synovial fluid from her left knee revealed numerous blast cells. Bone scintigraphy revealed increasing radiotracer uptake around the left knee, which suggested inflammatory arthritis. Arthritis, which was mitigated by chemotherapy and a follow-up bone scintigraphy, showed decreasing radiotracer uptake compared to the previous examination.

Conclusion: When treating patients with arthritis, it is important to consider a differential diagnosis of paraneoplastic arthritis or direct invasion by cancer.

Keywords: Leukemic arthritis; Seronegative arthritis; Paraneoplastic arthritis; Carcinomatous arthritis; Acute myeloid leukemia

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One type of arthritis associated with systemic diseases is paraneoplastic arthritis. Paraneoplastic arthritis or carcinomatous polyarthritis is seronegative arthritis[1]. The pathogenesis might be related to immune mechanisms such as cytokine or cytotoxic lymphocytes[2] which cannot be the result of direct invasion or compression of the tumor. It may precede cancer for less than one year or occur during the course of malignancy[3]. The patients usually resist standard treatment such as analgesic drugs or corticosteroids. The symptoms will improve after cancer treatment[4]. Most malignancy-associated arthritis is hematologic malignancy[5].

Acute myeloid leukemia is one of life-threatening hematologic malignancies which rarely present with arthritis. Unlike paraneoplastic arthritis, leukemic arthritis (LA) is an uncommon presentation in acute and chronic leukemias which proposed mechanisms are a local reaction to bony, periosteal, or capsular infiltration by malignant cells. LA occurs in 12% to 65% of childhood leukemia cases and 4% to 13% of adult leukemia cases[6]. LA can occur at any time during the course of leukemia and may be the first presenting manifestation. We report a 60-year-old acute myeloid leukemia patient presenting with chronic oligoarthritis.

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Case Report

A 60-year-old woman who had well-controlled diabetes mellitus type 2 and dyslipidemia presented with chronic oligoarthritis and unintentional weight loss for 3 months. At first, she got pain in her left ankle and both knees, with more severe pain on the

left side. She did not have morning stiffness or small joint pain. She went to the clinic and received an intra-articular corticosteroid injection in her left knee. One week later, she still had pain and went to the hospital, where she received an analgesic drug injection and underwent arthrocentesis, which was diagnosed as acute gouty arthritis. She received allopurinol 100 mg/day and colchicine 0.6 mg/day. The pain did not subside, and she continued to visit the doctor twice a week for analgesic injections. Two weeks after arthrocentesis, she came to our hospital with left ankle and both knees arthritis with ballottement test positive. Arthrocentesis was performed on her right knee, and the synovial fluid was mild turbid yellow with amount of 20 ml and showed inflammatory profile [White blood cell (WBC) 47,890 cell/mm^3, red blood cell (RBC) 300 cell/mm^3, neutrophil (PMN) 50%, lymphocyte (L) 9%, monocyte (M) 38% and normal sugar level], no crystal was seen, and the culture was negative for bacteria. Laboratory workups showed negative for rheumatoid factor, anti-CCP, HLA B27, ANA, and anti-dsDNA. Her complete blood count showed mild anemia with normal white blood cells and platelet counts. Prednisolone 30 mg/day was started and tried tapering off. One week later, she still had pain in her left knee and received another intra-articular corticosteroid injection. Two weeks later, the pain still existed, and prednisolone 20 mg/day was re-started. Two weeks later, she still had arthritis, and her doctor decided to add sulfasalazine 1,000 mg/day while continuing prednisolone 20 mg/day and allopurinol 100 mg/day. Two weeks later, she visited the hospital for an appointment, and her complete blood count showed leukocytosis, with young white blood cells being seen. She experienced fatigue and unintentional weight loss of 11 kg during this 2-months period with no fever. She denied chronic cough, photosensitivity rash, alopecia, oral ulcers, palpable mass over her body, or prior gastrointestinal or genitourinary tract infection. She was a non-smoker and a non-alcohol drinker. Her family did not have a history of malignancy or tuberculosis. Her current medications were allopurinol 100 mg/day, sulfasalazine 1,000 mg/day, calcium carbonate 1,000 mg/day, ferrous fumarate 600 mg/day, prednisolone 20 mg/day, vitamin D2 20,000 units/week, ezetimibe 10 mg/day, and metformin 850 mg/day. Her physical examination revealed an afebrile patient with pale conjunctiva, anicteric sclerae, impalpable lymph node, no abdominal tenderness, no hepatosplenomegaly, left knee and left ankle were swelling and tenderness. No skin lesions were seen. Cardiovascular and respiratory tract examinations were normal.

Investigations

Complete blood count (CBC) revealed WBC of 62.4x109/L (PMN 40%, L 11%, M 12%, eosinophil (E) and basophil (B) 0%, NRBC2 seen blast with auer rod and pronormocyte 9% promyelocyte 8%) which blast cell 20% was reported, hemoglobin (Hb) of 8 g/dL and platelet count of 169x109/L. Her peripheral smear showed myeloblast, normocytic red blood cells, no microangiopathic hemolytic anemia (MAHA) blood picture, adequate platelet counts and no polychromasia was seen. Her last CBC was 2 weeks before, WBC was 6.79x109/L (PMN 59.6%, L 18.4%, M 21.9%, E 0%, and B 0.1%), Hb 8.4 g/dL and platelet count 413x109/L. She had a normal coagulogram. Her blood test demonstrated high ESR (80 mm/hour), high C-reactive protein (7.54 mg/L), high lactate dehydrogenase (796 U/L), high uric acid (8.5 mg/dL), mild hypoalbuminemia (3.6 g/dL), no transaminitis, and normal bilirubin. Her renal function and electrolytes were normal. Radiologic examination of both knees showed narrowing of left knee joint space, no erosion or juxta-articular osteopenia was seen. Left knee arthrocentesis was done. Synovial fluid was mild turbid yellow with amount of 20 ml and showed an inflammatory profile with WBC 35,000 cell/mm^3 RBC 7,000 cell/mm^3, PMN 61%, L 5% M 31%, macrophage 3%, promonocytes and monoblasts were seen in synovial fluid wright stain. Flow cytometry was not done. Sugar in fluid was 85 mg/dL (Blood sugar was 108 mg/dL). Culture synovial fluid for bacteria was negative. Direct PCR for mycobacteria was negative. Her bone marrow biopsy revealed hypercellular marrow, approximately 80% with extensive involvement by atypical cells with immature nuclei, decrease of mature multilineage hematopoiesis, findings consistent with acute leukemia. Flow Cytometry from bone marrow showed blast 90.6% (monocytic gate 90.6%), HLA-DR+, CD117+, MPO+, CD 13+, CD 33+, CD 64+.

Bone marrow aspiration showed myeloblast 50% with dysmegakaryocyte + dysgranulocyte. Chromosome analysis was 46, XX.

Her bone scintigraphy revealed an area of increased radiotracer uptake at the left knee which corresponds to the arthritic process.

She was diagnosed with acute myeloid leukemia non M3.

Treatment

She decided to get induction chemotherapy

Table 1. CBC

	2/7/22	20/6/22	4/6/22	17/5/22	11/5/22	7/5/22	12/10/20	18/8/20
Hb	8	8.4	8.2	9.4	10.0	10.0	13.0	13.1
Blast	20.0							
ProMyelo	8.0							
Hct	27.7	28.7	26.7	31.4	32.4	32.7	39.6	39.9
MCV	91.1	92.6	87.0	87.2	85.9	83.8	78.3	78.1
MCH	26.3	27.1	26.7	26.1	26.5	25.6	25.7	25.6
MCHC	28.9	29.3	30.7	29.9	30.9	30.6	32.8	32.8
RDW	18.8	17.9	14.5	14.0	13.8	14.1	13.4	13.4
WBC	62.40	6.79	2.76	3.66	4.84	5.02	4.90	4.73
PLT	169	413	348	413	423	341	218	218
MPV	9.6	9.2	9.3	9.6	9.6	9.5	9.3	10.2
NE%	40.0	59.6	38.0	45.0	49.8	48.6	54.1	39.2
LY%	11.0	18.4	31.0	29.0	19.2	18.5	26.1	36.2
MO%	12.0	21.9	29.0	26.0	30.6	31.9	9.0	8.5
EO%	0.0	0.0	0.0	0.0	0.2	0.8	10.2	14.6
BA%	0.0	0.1	0.0	0.0	0.2	0.2	0.6	1.5
NRBC	2.0	5.0	0	0	0	0	0.0	0.0

Hb=hemoglobin [g/dL]; ProMyelo=promyelocyte [%]; Hct=hematocrit [%]; MCV=mean corpuscular volume [fL]; MCH=mean corpuscular hemoglobin [pg]; MCHC=mean corpuscular hemoglobin concentration [g/dL]; RDW=red blood cell distribution width [%]; WBC=white blood cell [x109/L]; PLT=platelet [x109/L]; MPV [fL]; NE=neutrophil; LY=lymphocyte; MO=monocyte; EO=eosinophil; BA=basophil; NRBC=nucleated red blood cells [/100 WBC]

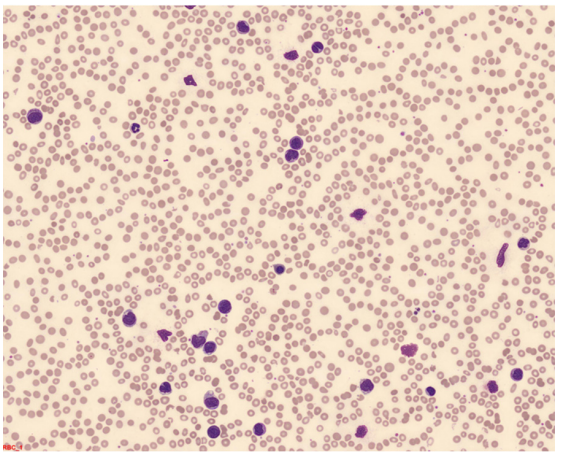

Figure 1. Peripheral blood smear.

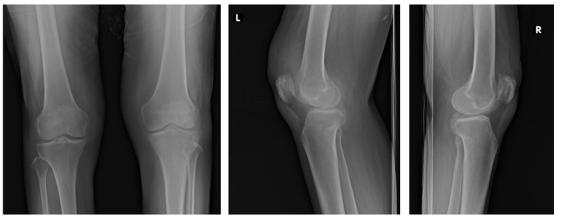

Figure 2. Radiologic examination of both knees.

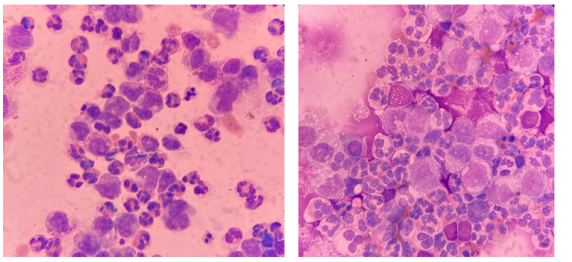

Figure 3. Left knee synovial fluid smear.

consisting of idarubicin 3 days and cytarabine 7 days regimen. Her arthritis subsided in a few days after finishing chemotherapy. She had febrile neutropenia at nadir phase and fully recovered.

Outcome and follow-up

Bone marrow examination after the complete first course of induction chemotherapy revealed morphologic complete remission, normocellular marrow and no increasing blast. Her bone scintigraphy showed a decreased degree of radiotracer uptake at the left knee, suggesting improvement of arthritic process but new arthritic process at the right first metatarsophalangeal joints (MTP) joint was seen. She did not have arthritis at the 1st MTP joint this time. She underwent ultrasound of those joints which showed chronic tophaceous gout at both 1st MTP joints. The consolidation phase of chemotherapy was introduced. High dose cytarabine was continued monthly. Unfortunately, after the first cycle of high dose cytarabine, she experienced severe infection from

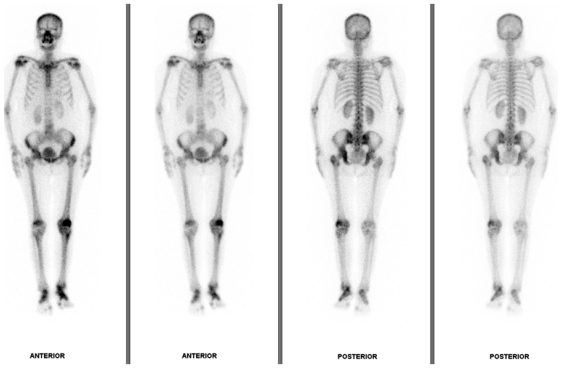

Figure 4. Bone scintigraphy (Tc-99m MDP) prior chemotherapy: No evidence of osseous metastasis, Suggested arthritic process at the left knee.

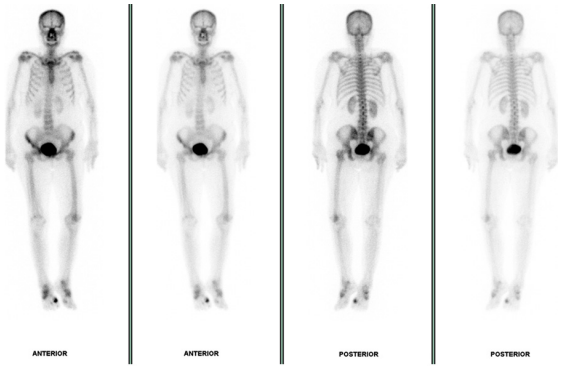

Figure 5. Bone scan (Tc-99m MDP) post chemotherapy 1 month: Suggested improvement of arthritic process at the left knee, Suggested new arthritic process at the right first MTP joint, No evidence of osseous metastasis.

pneumonia caused by multidrug-resistant Klebsiella pneumonia and Pseudomonas aeruginosa. Therefore, the second high dose of cytarabine was deferred. Her CBC was followed-up; no leukocyte blast presented. 3 months later, her disease relapsed. Her CBC showed WBC 158.03x109/L with blast 55%. She did not have arthritis symptoms. She was not eligible for any chemotherapy due to poor performance status and concurrent with infection. She passed away after 5 months of treatment.

Discussion

Our presenting patient, she had oligoarthritis which is resistant to anti-inflammatory drugs. She also had unintentional weight loss together with her joint pain. Her complete blood count did not show any abnormality except elevation of monocyte and mild anemia. After 2 months of follow-up, her WBC increased from 6.79 to 62.4x109/L with 20% blast cell and her platelet and red blood cell also decreased. Acute leukemia was suspected. Arthrocentesis left knee was done. The result showed blast cells in synovial fluid. We investigated bone marrow biopsy and flow cytometry. She was diagnosed with acute myeloid leukemia non M3. Her bone scan also showed inflammation of the left knee. After she got chemotherapy, her joint pain disappeared, and her bone scan improved.

Inflammatory arthritis is a rare presentation for malignancy. It can be due to immune reaction or direct invasion of tumor. Leukemic arthritis is more common in childhood leukemia. The proposed mechanisms for LA are a local reaction to bony, periosteal, or capsular infiltration by malignant cells[7]. LA mostly occurs in large joints, the patient may have pain out of proportion and negative serology for rheumatoid arthritis. LA can occur at any time during the course of leukemia and may be the first presenting manifestation. Looking back, we thought the patient might develop hematologic malignancy since her first arthritic symptom. Her CBC showed high monocyte count which could be seen in acute myeloid leukemia patients due to abnormal production of myeloid lineage white blood cells. Synovial fluid analysis also showed a high monocyte count, but it did not report any blast cell from central laboratory. So, we investigated the microscope by ourselves and blast cells in synovial fluid were seen. Her symptoms improved after leukemia treatment. Therefore, the etiology of arthritis in this patient might be from infiltrating malignant cells in synovial capsules then triggering an inflammatory process. After her leukemia was treated, her arthritis recovered. We did not do flow cytometry from synovial fluid due to inadequate specimen and synovial biopsy was not done due to an orthopedist suggesting that it might be false negative, and we should wait for bone marrow biopsy to make the diagnosis. The authors also found the tophi at her right 1st MTP which can be due to high uric acid from high turn overrate of malignancy cell.

What is already known on this topic?

Inflammatory arthritis is a rare presentation of malignancy but if the patients do not respond to conventional treatment, malignancy should be investigated.

What this study adds?

Synovial fluid cytologic examination under a microscope might help to differentiate blast cells from other cell types.

Initial abnormal CBC should be further investigated.

Acknowledgements

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Conflicts of interest

The authors declare no conflict of interest.

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