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Case Report

REACTIVE ARTHRITIS DURING INDUCTION PHASE THERAPY FOR ACUTE MYELOID LEUKAEMIA: GENETIC PREDISPOSITION DUE TO HLA B27

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Abstract :

We report a case of reactive arthritis during the induction phase therapy for acute myeloid leukaemia (AML) in a young lady with primary infertility. Klebsiella pneumoniae was isolated from her urine culture. Human leucocyte antigen (HLA) B27 positivity supported her genetic predisposition. We treated this patient with analgesics, antibiotics, and anti-inflammatory agents. Similar episodes recurred in consolidation therapy and there was involvement of previously uninvolved joint also. Early diagnosis with high index of suspicion is necessary for diagnostic workup in such cases and we recommend urinary cultures for identification of organism even in patients asymptomatic for urinary infection. It appears that there is common immunological, molecular and microbiological link between AML, HLA B27, reactive arthritis, Klebsiella and Infertility in this patient. Whether HLA B27 has any value in baseline workup of patients with AML prior to starting induction phase in patients with primary infertility needs more evaluation.

Keywords: Arthritis, Myeloid leukaemia, HLA B27

CASE REPORT

A 30 year old married (since 10 years) female presented with low grade fever, weakness, and fatigue since 3 months. There was no history of any habits or previous comorbidities. She was an extensively investigated case of primary female infertility but her menstrual history was normal. There was no history of any other medical illness in her. Her family history also was normal. Except for pallor her general examination was normal. Her systemic examination was normal.

Her investigations revealed haemoglobin (HB) 8.1 g/dL, total leucocyte count (TLC) 16400/µL with 6 % blast cells, 59% polymorphs, 34% lymphocytes, 13 % normoblasts and 1 % monocytes , platelet count (PLC) 99000/µL, total bilirubin (T.BIL) 0.98 mg/dL, alanine transaminase (ALT) 99 IU/L, aspartate transaminase (AST) 25 IU/L, alkaline phosphatase (ALP) 52 IU/L, random blood sugar 109 mg/dl, serum lactate dehydrogenase (LDH) was 1004 IU/L. Blood uric acid level was 2.48 mg/dL. Bone marrow examination showed hypercellular bone marrow with 51 % blasts. The blasts were medium in size with moderate nucleocytoplasmic ratio, fine diffuse chromatin and moderate amount of cytoplasm. Few myeloid precursors and polymorphs were seen along with mild dysmyelopoietic picture. Erythroid series showed normoblastic erythropoiesis with mild dyserythropoietic changes. Myeloid/erythroid ratio was altered. Megakaryocytes were not seen. PAS and Sudan black B stains were negative. The diagnosis was acute leukaemia. Immunophenotyping was positive for CD13 (83%), CD 33 (75%), CD7 (23%), CD117 (65%), MPO (6%), HLADR (54%), CD 19 (3%), CD 79a (2%), CD34 (2%), and negative for CD5, CD10, CD 22, Tdt (0%), thus

indicating myeloid immunophenotype. The final impression was acute myeloid leukaemia (AML) M2. Baseline 2-dimensional echocardiography, chest x-ray, ultrasonography of abdomen and pelvis were normal.

We treated this patient with 3+7 induction (daunorubicin 60 mg/m2 for 3 days and cytarabine 100 mg/m2 for 7 days). On post chemotherapy day (Þ) 4 she had right upper limb swelling involving fingers and forearm restricted below the cubital fossa. She was given adequate treatment with antibiotics. The swelling decreased in size but residual swelling persisted at index and middle finger.

She developed right knee swelling on Þ13. At this time her absolute neutrophil count (ANC) was 100/µL. She also had diarrhoea for 3 days. The magnetic resonance imaging (Fig. 1) showed joint effusion extending into supra and infrapatellar bursa with diffuse subcutaneous oedema involving lower thigh and around right knee joint. She was persistently febrile on Imipenem - Cilastatin combination and Vancomycin. Therefore she was started on Amphotericin-B but was still febrile after 72 hours hence was prescribed Colistin. On the treatment, this patient was simultaneously detected to have hyperglycemia and was put on insulin. The patient was stabilised and discharged on Þ 25. At this time her HB being 6.8 g/dL, TLC 3000/µL, ANC 1100/µL, PLC 64000/µL. She was discharged on oral metformin for her diabetes control.

On follow up visit swelling of her right middle and index finger and also that of right knee joint was present indicating persistent arthritis. C- reactive protein was positive, the value being 2.4 mg/dL. Rheumatoid factor was negative. Antinuclear antibody was positive in 1:40 dilution with speckled pattern which was insignificant.1

We also carried out Indirect immunofluorescent IgM test panel for atypical organisms namely Legionella pneumophilia serogroup1, Mycoplasma pneumonia, Coxiella burnetii, Chlamydia pneumonia, Adenovirus, Respiratory syncytial virus, Influenza A and B, Parainfluenza serotype 1, 2, 3 which all were negative. She had moderately elevated liver transaminases with normal bilirubin, the cause of which could not be determined. Viral markers for hepatitis A, B, C, E were negative. Removal of metformin from prescription normalised the liver function tests (LFT).2

We suspected the event as reactive arthritis (ReA) and did the work up for same and simultaneously shifted her to insulin from metformin. This patient was further put on oral prednisolone, doxycycline, and quinolones for arthritis. Meanwhile the urine culture showed positivity for Klebsiella pneumoniae which was extended spectrum beta lactamase (ESBL) positive. Hence she was prescribed sensitive antibiotics for 10 days. After 5 days she developed conjunctivitis. The symptom was eye discharge and on examination both upper palpebral conjunctiva showed mild papillae, eye discharge, trichiatic (misdirected) eyelashes. Thus completing the triad required for diagnosis of classical ReA syndrome. Also her Human leucocyte antigen (HLA B27) test by PCR method was positive. Further she was started on ophthalmic antibiotics and shifted to sulfasalazine as a disease modifying agent. Oral prednisolone was stopped and substituted with deflazocort in view of associated diabetes. Three phase bone scan of this patient revealed active metabolic changes to suggest active infection /inflammation changes in right hand joint with no definite abnormal uptake in right knee joint, however previous steroid administration might have masked the florid active changes in whole body scan.

The patient recovered with this event soon and the LFT also normalised. This episode delayed the consolidation of AML up to Þ50, thus causing a significant morbidity. We recommend the earliest suspicion of ReA for any arthritis following induction chemotherapy of AML and earliest urine culture to detect the causative organism and adequate treatment with the sensitive antibiotics, anti-inflammatory agents and disease modifying agents according to the status of arthritis for decreasing the days of morbidity.

HLA B27 carriers are known to predispose to inflammatory and autoimmune disorders. The incidence of HLA-B27 is increased in patients having acute leukaemia. For AML the relative risk (RR) is 1.67 and for acute lymphoblastic leukaemia (ALL) the RR is 1.68.3

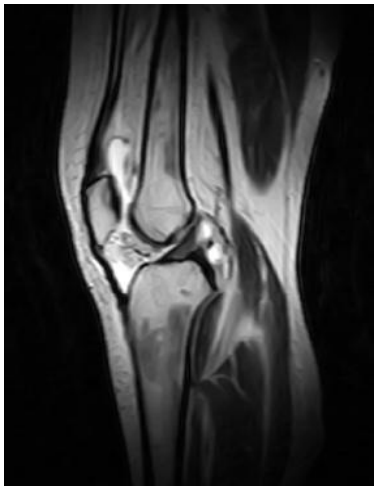

Fig 1.: The magnetic resonance imaging showed joint effusion extending into supra and infrapatellar bursa with diffuse subcutaneous oedema involving lower thigh and around right knee joint.

Induction phase of AML leads to neutropenia and is predisposed to various infections including bacterial infections of the intestinal and urinary tract. Any acute nonpurulent arthritis following some infection elsewhere in the body is known as ReA. There is a spectrum of this syndrome which is already reported in literature and also its association with chemotherapy of AML. 3-4

There is a reported case of atypical incomplete ReA syndrome (bilateral knee arthritis with keratoderma blennorrhagica) during the induction phase of AML with the chemotherapy regimen consisting daunorubicin, cytarabine and 6-thioguanine, where the causative organism was not detected and HLA-B27 was found to be positive. Also the patient had multiple episodes of similar events but with less severity in subsequent cycles of chemotherapy, finally with complete recovery.4

As compared to this, our patient had typical triad of the classical ReA syndrome. The causative organism was ESBL positive Klebsiella pneumoniae. As far as the diagnosis is concerned HLA-B27 is not required when complete triad is seen. It supports genetic predisposition if it is positive. So our patient had a genetic predisposition. Our patient has completed high dose cytarabine consolidation phase therapy. During consolidation chemotherapy cycles of high dose cytarabine she had joint symptoms which were less in severity than the symptoms in induction phase but there was involvement of right ankle joint also which was not involved in Induction phase therapy. At present this patient has completed the treatment protocol for AML and is on uneventful follow up for one year without any residual arthritis.

The classic triad of arthritis, nongonococcal urethritis, and conjunctivitis is now called as ReA.5

Bacteria causing ReA are usually enteric or venereal. In our case the pathogen was ESBL positive Klebsiella pneumoniae. There is evidence of immunological, molecular and microbiological link between Klebsiella and HLA B27. 6

Majority of the patients with ReA arthritis suffer from severe symptoms lasting weeks to 6 months. Predictors of chronicity are HLA-B27 positivity and triggering infections with Yersinia, Salmonella, Shigella or Chlamydia species.7

Symptoms of ReA occur within 1-3 weeks from onset of causative episode of urethritis/cervicitis or diarrhoea. The classic triad of symptoms has a sensitivity of 50.6% and a specificity of 98.9%.8

Initial therapy for joint symptoms is nonsteroidal anti-inflammatory drugs (NSAIDs). sulfasalazine or methotrexate are reserved drugs. The use of bacterial antigen enzyme potentiated desensitization immunotherapy is also found to be effective.8-12

One unusual observation in this case is the history of infertility preceding the ReA, also Chlamydia test being negative arises a suspicion of direct genetic predisposition of the patient to infertility as well as reactive arthritis probably through HLA B27. Usually the reported sequence is Chlamydia induced urinary tract or sexually acquired infection leading to ReA and infertility.13

For any arthritis following induction phase chemotherapy of AML, the possibility of ReA should be kept in mind. All possible site cultures including urine culture should be done to detect the organism. Treatment should be started earliest and should be administered for adequate time with confirmation of negative culture reports. There is possibility of common immunological, molecular and microbiological link between AML, HLA B27, ReA, Klebsiella and Infertility in this patient. It may through molecular mimicry. Though more evidence is needed for confirmation of association of infertility and HLA B27, we suspect baseline HLA B27 testing might predict possible reactive arthritis if the physician comes across the patient with similar history of primary infertility. 12

References:Authors' Disclosures of Potential
Conflicts of Interest:The authors indicated no potential conflicts of interest.

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