

## Case Report

## Human Leukocyte Antigen-B27: The Genetic Predisposition Leading to Reactive Arthritis during Induction Phase Chemotherapy for Acute Myeloid Leukemia

### Abstract

We report a case of reactive arthritis (ReA) during induction phase chemotherapy of a 15-year-old male patient with acute myeloid leukemia (AML) M4 with inv(16), most probably due to a genetic predisposition of being human leukocyte antigen b27 (HLA-B27) positive. The episode of ReA recurred during consolidation therapy; however, the patient was asymptomatic after the completion of treatment. The link between HLA-B27 and a large family of inflammatory rheumatic diseases is a well-established fact, but interestingly, there is also a molecular link between HLA-B27 and hematological malignancies. This case brings to our notice, the common immunological, molecular, and microbiological link between AML, HLA-B27, and ReA. It also emphasizes the fact that clinicians should have a high index of suspicion of HLA-B27 positivity, if a case of AML develops arthritis during chemotherapy, since early introduction of immunosuppressive medications for arthritis may reduce morbidity and prevent delay in the administration of further chemotherapy cycles.

**Keywords:** Acute myeloid leukemia, arthritis, human leukocyte antigen B27

### Introduction

The link between human leukocyte antigen B27 (HLA-B27) and a large family of inflammatory rheumatic diseases is a well-established fact.<sup>[1,2]</sup> Reactive arthritis (ReA) is defined as an immune-mediated synovitis resulting from slow bacterial infections and showing intra-articular persistence of viable nonculturable bacteria and/or immunogenetic bacterial antigens synthesized by metabolically active bacteria residing in the joint and/or elsewhere in the body.<sup>[1]</sup> Several large-scale studies have reported that HLA-B27 carriers may have an increased predisposition of hematological malignancies.<sup>[2-4]</sup> Interestingly, we are reporting a case of 15-year-old male with acute myeloid leukemia (AML) who developed ReA during induction chemotherapy and was positive for HLA-B27. There are very few case reports in literature with a similar constellation of findings. This case emphasizes the fact that HLA-B27-associated genetic predisposition should be considered in patients with leukemia and unexplained arthritis.

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### Case Report

A 15-year-old male presented with a history of fever and progressive pallor for 3 months. There was no prior history of any rheumatological disorder. On examination, he was pale and had multiple petechiae, purpura, and ecchymotic patches. Systemic examination revealed significant hepatosplenomegaly. On investigations, his complete blood count showed Hb of 8.3 g/dl, white blood cell count of 45,300/mm<sup>3</sup>, platelet count of 32,000/mm<sup>3</sup>, and peripheral smear showed 54% blasts. Bone marrow was hypercellular with 65% blasts with monocytic differentiation on morphology. Flow cytometry confirmed the diagnosis of AML, and cytogenetics showed inv(16) in 80% cells. Thus, a diagnosis of AML (FAB-M4 subtype) with inv(16) was established. He was put on induction chemotherapy for AML consisting of 7 days of cytarabine at a dose of 100 mg/m<sup>2</sup> and 3 days of daunomycin at 60 mg/m<sup>2</sup>. On day 6, he developed severe pain and swelling of both the knee joints associated with redness and restriction of movements [Figures 1 and 2]. Gradually, it progressed

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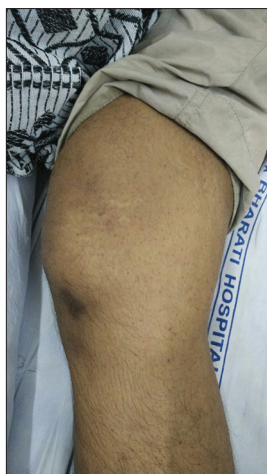


Figure 1: Arthritis of knee joint



Figure 2: Arthritis of ankle joint

to the ankle and wrist joints. Ultrasonography of the knee joints revealed joint effusion extending into supra- and infra-patellar bursa. On day 10, he developed febrile neutropenia along with worsening of the arthritis. Blood culture was sent, and he was put on intravenous antibiotics. Meanwhile, he required multiple blood and platelet transfusion support. Initially, his symptoms were attributed to either septicemia or immune reactions to transfusions. Subsequently, the blood culture grew *Klebsiella*, sensitive to meropenem and amikacin, and he was put on these antibiotics accordingly. Although his fever responded to antibiotics and neutrophil count recovery, his arthritis did not recover in spite of treatment with analgesics and anti-inflammatory agents. A possibility of ReA predisposed due to HLA-B27 positivity was considered. HLA-B27 done by the polymerase chain reaction method was reported as positive. He was put on prednisolone to which he showed significant improvement within four days, and hence, it was stopped in 8 days. He developed similar symptoms but of less severity during the consolidation therapy. He again required steroids for the control of symptoms. This time, we continued low dose of prednisolone during the three consolidation cycles of high-dose cytarabine. After the completion of therapy, steroids were tapered and stopped over a period of 20 days. At follow-up visit of 9 months after completion of chemotherapy, he continues to be in remission and free of any symptom of arthritis.

## Discussion

The three main aspects of the pathogenesis of ReA are the presence of bacteria or bacterial products in the joint, the interaction between bacterium and host, and the local immune response directed against these bacteria.<sup>[1,4,5]</sup> HLA B27 carriers are predisposed to ReA due to the affinity of HLA B27 to arthritogenic peptides and its ability to present these potentially arthritogenic peptides to cytotoxic T-lymphocytes.<sup>[4,5]</sup> HLA-B27 carriers are also at an increased risk of acute leukemias.<sup>[2-4]</sup> In a large-scale study

by Au *et al.*, the relative risk in HLA-B27 carriers for acute lymphoblastic leukemia and AML was reported to be 1.68 and 1.67, respectively. The correlation was statistically significant.<sup>[3]</sup> The various explanations for such HLA leukemia association include reduced immune surveillance, molecular mimicry by oncogenic microbes, or linkage disequilibrium with unidentified susceptibility genes.<sup>[3,6]</sup> HLA plays an important role in immune surveillance, and HLA polymorphisms may affect the ability of the immune system to recognize the malignant cells and target them for elimination by T cells.<sup>[6]</sup> There are several case reports of rheumatic manifestations following autologous SCT in HLA-B27-positive individuals.<sup>[7]</sup> However, very few cases of ReA during induction therapy for AML due to HLA predisposition have been described in literature.<sup>[5]</sup> Another remarkable aspect of this case was that the blood culture of the patient grew *Klebsiella*, and a molecular mimicry theory has been postulated for association between an amino acid sequence in HLA-B27 and *Klebsiella* products according to which rheumatic manifestations may result from a cross-reactive antibody response between a unique portion of HLA-B27 and certain bacterial epitopes.<sup>[8]</sup> To conclude, this case brings to our notice, the common immunological, molecular, and microbiological link between AML, HLA-B27, ReA, and *Klebsiella*. It also highlights the fact that HLA-B27 predisposes to ReA during the induction therapy for AML, and considering the molecular link between HLA-B27 and hematological malignancies and relatively high incidence of HLA-B27 in Asian Indian males, it may be considered as a baseline investigation before initiation of induction therapy in AML treatment as early introduction of anti-inflammatory and immunosuppressive medications for arthritis may reduce morbidity and prevent delay in the administration of further chemotherapy cycles.<sup>[9]</sup> Another issue that needs to be considered in the management of ReA during chemotherapy is the importance of prolonged course of targeted antibiotics for eradication of bacteria responsible

for ReA which are frequently intracellular to prevent subsequent flare up of ReA.<sup>[10]</sup>

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### Conflicts of interest

There are no conflicts of interest.

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