

CASE REPORTS

FIRST REPORTED CASE OF MAJEED SYNDROME FROM PAKISTAN

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ABSTRACT

Majeed syndrome, characterized by chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia, is a rare disease reported in children. We report a case of Majeed Syndrome in a 9-year-old boy, born of consanguineous marriage reporting to us for treatment of anemia, requiring blood transfusion. He underwent below-knee-amputation due to un-resolving recurrent osteomyelitis at multiple sites. There was history of pain insensitivity and fever during hot weather as well. His interleukin-6 levels were raised. This is the first case of Majeed Syndrome from Pakistan and first in the world with Hereditary Sensory Autonomic Neuropathy type 4 as an associated feature.

Keywords: Anakinra, Chronic recurrent multifocal osteomyelitis, Interleukin-6, LPIN2 mutation, Majeed syndrome.

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INTRODUCTION

Majeed syndrome is an autosomal recessive, auto-inflammatory disorder distinct from non-syndromic Chronic Recurrent Multifocal Osteomyelitis (CRMO). It has a variable age of onset with numerous relapses and remissions.¹ Long bones are most commonly involved; however, less commonly pelvic and vertebral bones may as well be involved. So far, reported extra-skeletal features include Congenital Dyserythropoietic Anemia (CDA) with a microcytic and hypochromic picture, neutrophilic dermatosis (sweet syndrome), psoriasis, severe acne, crohns disease, ulcerative colitis, palmoplantar pustulosis, granulomatous polyangiitis, takayasu arteritis.² Early and correct recognition of this syndrome will lead to timely initiation of proper treatment, prevention of futile therapies due to misdiagnosis and reduction in long-term morbidity. Here, we report a case of 9-year-old boy that underwent a below-knee-amputation (BKA) due to suspicion of infective etiology for the non-resolving osteomyelitis.

CASE REPORT

The 9-year-old was born by spontaneous vertex delivery at full term. He was fourth among six siblings, product of a consanguineous marriage. All his siblings were healthy and there was no history of any musculoskeletal disease in the immediate or extended family. He was vaccinated as per the Extended Program of Immunization. His early motor milestones were slightly

delayed but eventually achieved. He had his first episode of osteomyelitis at the age of two years in his left foot that gradually progressed to involve other bones of his lower limbs. He eventually lost mobility at eight years of age. He had long-standing anemia requiring off and on blood transfusions without any history of bleeding from any site. There was also history of episodic hyperthermia which occurred during hot weather and was associated with anhidrosis.

There was no history of any bowel or bladder complaints, malabsorptive disorder, feeding difficulty, esophageal dysmotility, breathing difficulty, emotional lability and alacrima or exposure to tuberculosis.

He was under treatment of various physicians who suspected immunodeficiency but all his tests including nitroblue tetrazolium reduction test and oxidative burst using dihydrorhodamine stain were normal. Lymphocyte subset analysis and immunoglobulin levels were also within normal limits. He underwent a Below Knee Amputation (BKA) for non-resolving chronic osteomyelitis at the age of seven years.

On examination, he was an intellectually sound, friendly boy with disability of level IV on the Gross Motor Functional Classification Scale. His length was 108 cm and weight 20 kg which were well below the third centile for his age and gender. Fronto-occipital circumference was 48.7 cm. He was pale but there were no findings on cardiovascular, respiratory or abdominal examination. His left leg was amputated below the knee and his right leg had lost normal bony and joint configuration around the knee due to recurrent

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episodes of osteomyelitis (Figure-1). There was no tenderness and power was 5/5 in the upper and lower limbs. Knee reflex was not elicitable in the right leg due to resorption of tendons and surrounding tissues and in the left leg due to an ulcer 6x7 cm on the overlying skin. Ankle jerk was elicited in the right leg. The child had limited mobility and would crawl across the room with the help of his upper limbs. He had hypertrophic calluses on his hands and acroosteolysis of his distal phalanges (Figure-2). The child also had

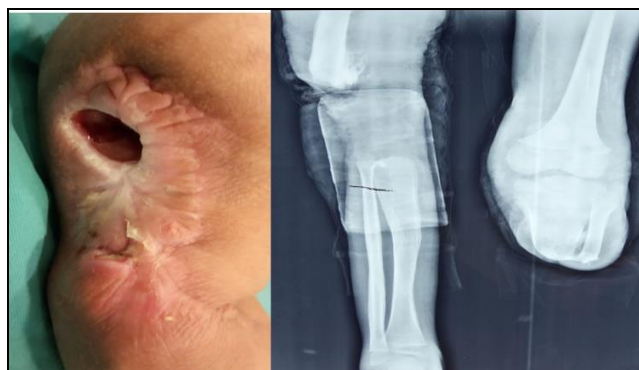


Figure-1: Image of patient's right leg showing an open wound that exposes underlying tissues and bone. X-ray of the same leg showing resorption of distal femur, proximal tibia and complete resorption of patella. Distal femur shows cortical thickening, periosteal reaction and soft tissue edema. Cortical irregularities are also appreciated in the tibial epiphysis and metaphysis. Left leg has been amputated below the knee.

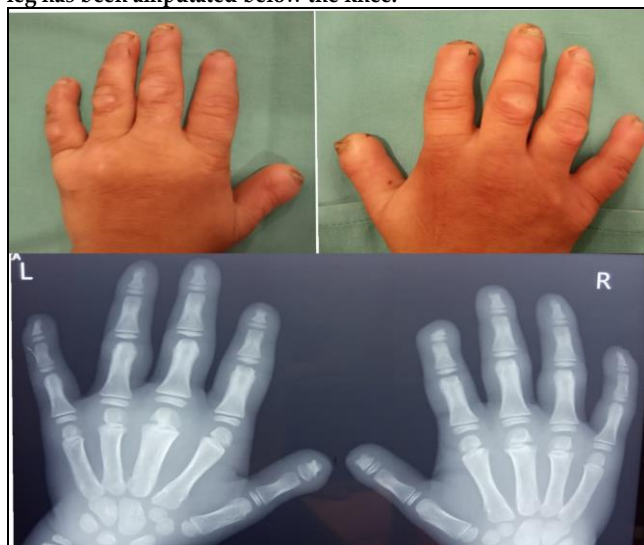


Figure-2: Metacarpals of the left hand show lytic lesions with cortical thickening. Distal phalanges show bony resorption on both hands.

hypodontia. Eruption of teeth was at appropriate ages but later shed without any trauma or pain. There was generalized lymphadenopathy. All lymph nodes were mobile, non-matted and non-tender. The largest lymph

node was in the inguinal region, measuring more than 4cm in the long axis.

Laboratory investigations revealed hypochromic, microcytic anemia (hemoglobin: 5.6 mg/dL) and a total leukocyte count of $8.5 \times 10^9/L$ and platelet count of $114 \times 10^9/L$. Peripheral blood film demonstrated anisopoikilocytosis. Erythrocyte Sedimentation rate (ESR) was 24 mm at first hour (normal <9) and C-Reactive Protein (CRP) was 48.5 mg/dL (normal <10 mg/dL). IL-6 levels were 12.83 pg/ml (normal <7). However, blood cultures did not yield the growth of any organism. There was no evidence of any hepatic, renal or pulmonary dysfunction. Creatinine phosphokinase levels, tuberculin skin test and urine and stool analysis were normal. Antinuclear antibodies and Rheumatoid factor was negative. Vitamin B12 levels were 675 (normal: 176-686 pmol/L) and folate levels were 19.9 (normal: 6.26-45.3n mol/l). Abdominal ultrasound and echocardiography were normal.

Contrast enhanced Magnetic Resonance Imaging (MRI) of the lower limbs revealed resorption of distal part of right femur, patella and knee joint bones. There was abnormal signal intensity with post contrast enhancement of soft tissues of right thigh. Muscles had been partially replaced by fatty tissue. Left thigh also had abnormal T2W/STIR hyperintense signal in the distal portion anteriorly, around the knee joint and anterior to the tibia. There were abnormal signal intensity areas in the left tibial epiphysis and metaphysis and gross knee joint effusion. Bone scan revealed increased uptake at multiple foci in the lower limbs.

Electromyographic nerve conduction studies being normal, a clinical diagnosis of HSAN type 4 was made. Insertional irritability was completely absent during the study. Labs were not suggestive of any immunodeficiency as already mentioned except IgG and C3 levels were raised consistent with chronic inflammation. Genetic studies were not available in our set up.

The patient was started Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and tab prednisolone at 1 mg/kg/day. Injection pamidronate at 1.5 mg/kg/day for 2 days every 3 months was also prescribed. Patient was also advised regular physiotherapy for prevention of contractures. High dose methyl prednisolone, methotrexate were reserved as secondary options. Anakinra was planned to be started.

DISCUSSION

Majeed syndrome was first reported by Majeed *et al*, in three children of one family of Arab origin.³ Our

case is the first reported with HSAN type,⁴ in the absence of positive family history.

Its etiology has been discovered to be genetic in origin with an autosomal recessive pattern. Ferguson *et al*, attributed the condition to homozygous mutation in LPIN.² The gene was mapped to the short arm of chromosome 18. LPIN2 was found to be expressed in all body tissues in this study on 6 individuals.⁴

The phenotypic features include the triad of bone inflammation, CDA with microscopic and hypochromic picture and recurrent fevers. It is distinct from the non-syndromic CRMO. The co-existence of CRMO with other dermatological conditions and inflammatory bowel disease and its response to steroids further potentiates its autoimmune pathogenesis.⁵ Disease onset is mostly in the 2nd or 3rd year of life. However, few cases have been reported in the infantile and late adolescent period.^{1,6}

Laboratory findings are nonspecific except raised ESR and CRP being the most consistent. Patients express increased levels of IL-1B and IL-6 on their monocytes⁷. Whole body imaging with a 99 m technetium scan helps detect occult lesions. MRI however, helps avoid unnecessary radiation exposure in a child with otherwise obvious clinical diagnosis of the syndrome. Lesions appear hyperintense on T2 weighted images with associated soft tissue inflammation. Biopsy specimens may show acute, subacute and chronic lesions mixed at the same site.⁵

Treatment consists of supportive agents such as NSAIDs, oral and monthly intravenous pulse doses of steroids and intravenous bisphosphonates every 3 months to prevent osteoporosis. Physiotherapy to maintain muscle strength and prevent formation of flexion contractures remains an important cornerstone of the management plan. Definitive therapeutics includes methotrexate, etanercept (TNF inhibitor) and anakinra (IL-1 receptor antagonist). Due to the rarity of this disease no multicentre trials have been conducted for this disease. However, there are case reports showing efficacy of anakinra in reducing both the symptomatology of the disease as well as the inflammatory markers such as ESR, CRP, IL-1 and IL-6 levels.^{8,9} Infliximab and canakinumab have variable therapeutic outcome. Dosing interval of 6 weeks or shorter may be more effective.¹⁰ Prevention of future cases includes genetic

testing for possible carriers in the family and prenatal testing during pregnancies.

Prognosis of CRMO (both syndromic and non-syndromic) among paediatric patients depends on various factors including the severity of disease. Females with unifocal involvement usually have a better prognosis as compared to males with multifocal involvement.

Disclosure

Informed consent was obtained from the parents of the patient to publish this case.

Conflict of Interest: None.

Authors' Contribution

QUM: Direct contribution, AR: Direct contribution, FI: Direct contribution, MS: Direct contribution, UA: Intellectual contribution, MTK: Intellectual contribution.

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