Seronegative Polyarticular Juvenile Idiopathic Arthritis: A Case Report.

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ABSTRACT:
Juvenile idiopathic arthritis (JIA) is a chronic rheumatologic childhood disorder of unknown etiology usually presenting with peripheral arthritis. Usually involving the small joints symmetrically, polyarticular JIA is characterized by involvement of 5 or more peripheral joints and is further categorized depending on RA Factor positivity. We aim to report a case of seronegative polyarticular JIA to increase awareness regarding this disease. A 15-year-old boy presented with 3-month history of bilateral symmetrical joint pains, swelling and morning stiffness lasting 3-4 hours. For his ankle and knee pain, he had consulted a local doctor who suspected Rheumatic Fever and started penicillin and analgesics resulting in minimal improvement. He was a student but was unable to attend school in last 2 months due to this illness and had become bed-bound for last 2 weeks. On examination, there was swelling and tenderness of ankles, knees, elbows, wrists, metacarpophalangeal and proximal interphalangeal joints bilaterally. On investigation, ESR, CRP and serum ferritin were raised with normal complete blood count, urinalysis, liver and renal function tests, ASO test, blood and urine cultures, TSH, serum CPK and serum aldolase. Echocardiography did not reveal any abnormalities. His ANA, RA factor and Anti-CCP antibodies were negative. He was diagnosed with Seronegative Polyarticular Juvenile Idiopathic Arthritis and started on oral prednisolone and methotrexate. Currently the patient is asymptomatic on methotrexate 20mg/week. Our patient with symmetrical polyarthritis had negative ANA, RA Factor and Anti-CCP antibodies leading to a diagnosis of seronegative polyarticular JIA. Early screening and prompt management of JIA is required to improve prognosis and reduce risk of disability. The differential diagnosis of childhood joint pains is wide and variable including diseases of autoimmune, cardiac and haematological systems. For diagnosis of JIA, arthritis persisting for more than 6 weeks with onset of symptoms prior to 16 years of age is required with exclusion of secondary causes of joint inflammation.

Keywords: Juvenile Idiopathic Arthritis, ANA, RA Factor, Anti-CCP antibodies, Methotrexate.

Introduction:

Juvenile idiopathic arthritis (JIA) is a chronic rheumatologic childhood disorder of unknown aetiology usually presenting with peripheral arthritis. For diagnosis of JIA, arthritis persisting for more than 6 weeks with onset of symptoms prior to 16 years of age is required with exclusion of secondary causes of joint inflammation.[1] According to the International League of Associations for Rheumatology (ILAR) depending on the clinical features and pattern of joint involvement, JIA is classified into 7 sub-types: Systemic juvenile idiopathic arthritis (sJIA), also known as systemic-onset JIA (SoJIA), seropositive polyarticular JIA, seronegative polyarticular JIA, oligoarticular JIA, juvenile psoriatic arthritis (JPsA), Enthesitis-related arthritis (ERA) and undifferentiated JIA.[2] Usually involving the small joints symmetrically, polyarticular JIA is characterized by involvement of 5 or more peripheral joints and is further categorized depending on RA Factor positivity.[3] Being more common in females, seronegative polyarticular JIA shows a biphasic incidence with peaks at 2-4 years and 6-12 years of age.[3] In later childhood and adolescence, seropositive polyarticular JIA is more frequent.[4] Cervical spine, hip and shoulder joint involvement may also been seen and temporomandibular arthritis leading to secondary microretrognathia has also been reported.[5] Other clinical features may include low-grade fever, weight loss, anaemia, hepatosplenomegaly and growth retardation.[6,7] Chronic inflammation of the joints leads to limitation of patient's routine activities and productivity. RA factor and Anti-CCP antibody positivity and hip joint involvement are linked to high joint morbidity, deformity and disability.[3,8] It should be noted that there is an increased risk of uveitis in JIA which may be asymptomatic and lead to vision loss if untreated. The risk factors for development of uveitis in JIA include oligoarticular joint involvement, female sex, ANA positivity, young age of disease onset and HLA-DRB1*0801.[4]

Case Description:

We report the case of a 15-year-old boy who presented with a 3-month history of joint pains and swelling predominantly. affecting his ankles, knees, elbows and hand joints associated with morning stiffness lasting 3-4 hours. The joint involvement started initially from the right ankle, progressively involving the left ankle and both knees leading to difficulty in walking to the extent that he had become bed -bound for the last 2 weeks. On Visual analogue scale, he reported 9/10 pain in his ankles and knees while 5/10 pain in his elbows and hand joints. There was no history of fever, sore throat, skin rashes, oral or genital ulcers, alopecia, altered bowels, Raynaud's phenomena, muscle weakness, red eye, palpitations, chest pain or shortness of breath. For his ankle and knee pain, he had consulted a local doctor who suspected Rheumatic Fever and started penicillin and analgesics resulting in minimal improvement. He was a student but was unable to attend school in last 2 months due to this illness. There was no history of smoking, alcohol intake, illicit drug abuse or sexual contact. There was no family history of arthritis, psoriasis or autoimmune disorders. On examination, he was vitally stable with temperature 98.5°F. Joint examination revealed swelling and tenderness of ankles, knees, elbows, wrists, metacarpophalangeal and proximal interphalangeal joints bilateral-

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ly. There was no spinal tenderness with normal range of spinal movement. Cardiac, respiratory and abdominal examinations were normal.

On investigation, ESR, CRP and serum ferritin were raised at 45mm/hour, 24mg/dl and 989ng/ml respectively. His complete blood count, urinalysis liver and renal function tests were within normal limits as shown in Table 1. ASO test, blood and urine cultures were negative. His TSH, serum CPK and serum aldolase were normal. Serologies for syphilis, HBV, HCV and HIV were negative. A chest X-ray and abdominal ultrasound were within normal parameters. His echocardiography did not reveal any abnormal valve defects or vegetations. An autoimmune profile compromising ANA, RA factor and Anti-CCP antibodies was negative. Slit-lamp examination was negative for uveitis. He was diagnosed as having Seronegative Polyarticular Juvenile Idiopathic Arthritis and started on oral prednisolone (10mg/day) and oral methotrexate (7.5mg/week) in addition to oral and topical NSAIDs, oral omeprazole, folic acid, calcium and vitamin D supplements. At follow-up at 4 weeks, he was moderately improved in majority of the joints, but still complained of significant pain and swelling of right ankle. After discussing with the patient and his parents, intra-articular methylprednisolone acetate 40mg was injected in right ankle along with increasing dose of methotrexate. On his subsequent follow-up he had improved markedly and his steroids were tapered and gradually stopped. Currently the patient is asymptomatic on methotrexate 20mg/week and has suffered no adverse effects of therapy.

Table 1: Initial blood work-up of the patient

Investigation	Patient's Value	Reference Range
Hemoglobin (G/dl)	12.9	12.0-16.0
TLC (per mm^3)	10.7	4,000-11,000
Platelets (per mm^3)	386	150,000-450,000
Hematocrit (%)	37	35-46
MCV (fL)	83	77-91
MCH (pg.)	28	26-32
MCHC (G/dl)	34	32-36
ESR (mm/hour)	45	Up to 20
CRP (mg/dl)	24	Up to 5.0
Blood Urea (mg/dl)	36	10-50
Serum Creatinine (mg/dl)	0.5	0.6-1.4
Albumin (G/dl)	4.5	3.5-5.0
Globulin (G/dl)	2.7	1.8-3.2
Serum Bilirubin (mg/dl)	0.2	up to 1.0
AST (U/L)	34	Less than 35
ALT (U/L)	33	Less Than 35
Alkaline Phosphatase (U/L)	109	30-120
Serum CPK (mcg/L)	72	10-120
Serum Aldolase (U/L)	6.8	1.0-7.5
Serum Ferritin (ng/ml)	989	24-336
TSH (iIU/ml)	1.6	0.35-4.95

Discussion:

For diagnosis of JIA, arthritis persisting for more than 6 weeks with onset of symptoms prior to 16 years of age is required with exclusion of secondary causes of joint inflammation.[1] Our patient had disease onset at 15 years of age and had persistent arthritis for 12 weeks at presentation. Furthermore, this workup of other secondary causes such as infections, rheumatic fever, haematological malignancy and thyroid dysfunction were negative helping to establish diagnosis of JIA. Polyarticular JIA is characterized by involvement of 5 or more peripheral joints and is further categorized depending on RA Factor positivity.[3] Our patient had involvement of bilateral ankles, knees, elbows, wrists, metacarpophalangeal and proximal interphalangeal joints with a negative RA factor thus confirming the diagnosis of seronegative polyarticular JIA. Seronegative polyarticular JIA shows a biphasic incidence with peaks at 2-4 years and 6-12 years of age and is more common in females.[3] This was in contrast to our patient who was a male and had disease onset at 15 years of age. Furthermore, our patient did not experience any extra-articular clinical features of JIA. Predictors of good prognosis in our patient included negative RA factor, Anti-CCP antibodies and lack of hip involvement. Having a normal slit-lamp examination, our patient was at low risk of developing uveitis due to his male sex, polyarticular joint involvement, ANA negativity and older age of disease onset.

The aim to treatment in JIA is multidimensional and encompasses pain control, preservation of range of motion and muscle function, induction of disease remission, managing systemic complications and facilitation of normal psycho-physical development.[3] Adverse effects of the drugs should also be considered. The traditional initial approach is with NSAIDs such as ibuprofen, indomethacin or naproxen.[9] Oral corticosteroids such as prednisolone are often used due to their strong anti-inflammatory effects in controlling joint inflammation. However, their use is often limited by their numerous adverse effects. Intra-articular corticosteroids such as methylprednisolone and triamcinolone have also been shown to be effective in achieving disease remission.[10] Conventional DMARDs employed in treatment of JIA include methotrexate, sulfasalazine and leflunomide.[9,11] Methotrexate is a folate antagonist and clinical effect is usually seen within 2-3 weeks of treatment initiation. Folic acid at dose of 1mg/day is usually co-prescribed to reduce the risk of adverse effects of methotrexate such as nausea, bone marrow suppression, oral ulcers and hair loss.[3] In case of severe or refractory disease not responding to corticosteroids and conventional DMARDs, biological DMARDs are prescribed to achieve disease remission. The biological DMARDs used in JIA include TNF-alpha inhibitors (etanercept, adalimumab, infliximab), IL-1 antagonists (anakinra, canakinumab), IL-6 antagonist (tocilizumab) and anti-CD20 agents (rituximab).[12-14] Our patient had minimal response to NSAIDS but responded well to oral prednisolone and methotrexate. He required intra-articular injection once to right ankle. Currently he is in remission on methotrexate 20mg/week and suffered no adverse effects.

In conclusion, JIA is a chronic rheumatologic childhood disorder of unknown aetiology usually presenting with peripheral arthritis. Our patient with symmetrical polyarthritis had negative ANA, RA Factor and Anti-CCP antibodies. A diagnosis of seronegative polyarticular JIA was established and he was managed with prednisolone and methotrexate resulting in marked improvement. Early screening and prompt management of JIA is required to improve prognosis and reduce risk of disability. The differential diagnosis of childhood joint pains is wide and variable including diseases of autoimmune, cardiac and haematological systems. For diagnosis of JIA, arthritis persisting for more than 6 weeks with onset of symptoms prior to 16 years of age is required with exclusion of secondary causes of joint inflam-

mation. A high index of clinical suspicion is required to timely diagnose JIA to reduce complications and morbidity.

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