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Case Report

Systemic juvenile rheumatoid arthritis in an 11 year old boy: a case report

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Juvenile rheumatoid arthritis (JRA) is the most common rheumatic condition in children and a major cause of chronic disability.[1] JRA is defined as persistent arthritis in one or more joints for at least six weeks, when certain exclusionary conditions have been eliminated.[2,3] The three major subtypes of JRA are based on the symptoms at disease onset and are designated as systemic onset, pauciarticular onset, and polyarticular onset.[2] Systemic onset juvenile rheumatoid arthritis (SoJRA) represents about 10–20% of all forms of JRA.[4]

The incidence of JRA is approximately 13.9/100,000 per year among children 15 years old or younger.[1] In Finland, the incidence was 19.5/100,000 of the population under 16 years of age. The incidence was significantly higher than in earlier years (1980, 1985, and 1990) in the same district.[5] Different racial and ethnic groups appear to have varying frequencies of the subtype of JRA.[1]

The treatment of JRA is achieved using combinations of anti-inflammatory and immunomodulatory medications in combination with physical and occupational therapy, occasional surgery, nutritional support, and psychosocial and educational partnerships with patients and parents.[3,6] It is widely thought that a comprehensive team approach is associated with a superior outcome.[7] This paper reports a case of systemic JRA in an 11-year old boy.

The case

An 11-year old boy attended the Emergency Department, Sanglah Hospital, Denpasar, Indonesia, on July 4th 2006 with joint pain that had first appeared four days before. The joints involved were ankles, wrists, knees, and fingers; they were painful and accompanied by redness, swelling, and a warm sensation. The patient was unable to walk, complained of stiffness in the ankles, knees and wrists, which was more pronounced in the morning. There was a fluctuating high fever. One day before admission, the subject also reported vomiting 4-5 times. The subject was prescribed chloramphenicol, piroxicam, dexamethasone, and paracetamol. The fever and pain decreased shortly after taking the medication but increased again a few hours later. There was no swelling of the eyes or other organs. Urination and defecation were within normal limits.

The history of illness started four years ago. Many joints were affected, including the knees, elbows, wrists, ankles, and fingers, where all of the

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inter phalanx joints were involved. The affected joints also felt warm, looked red, and were swollen. The pain was more prominent when the joints were active. The subject's complaints continued periodically and disappeared after receiving medication but reappeared after some time. Each attack lasted two months. To help decrease the pain, his mother reported that during the two months before admission, she would often buy additional medication such as ibuprofen syrup as well as a traditional herbal medicine. The subject is the eldest of two siblings. There was no family history of similar problem.

On physical examination, the patient was alert and had a regular pulse rate of 104 beats per minute. The respiratory rate was regular at 24 beats per minute, axillary temperature was 36^0C, and blood pressure was 105/85 mmHg. His body weight and height were 30 kg and 130 cm respectively, well-nourished.

The patient presented with a moon face (cushingoid appearance), with no palpebral edema, no pale and no jaundice. Examination of the lower extremities showed pes valgus of the left foot, with the knee and ankle being swollen, tender, red, and painful on motion. The rest of the examination was normal.

Laboratory investigation revealed a leukocyte count of 30,200/μL, neutrophil 89.9%, lymphocyte 8.2%, hemoglobin 12 g/dL, hematocrit 38.9%, and platelet count 485,000/μL. ESR was 15 mm/hour, and CRP was 384 mg/L. Examination of RF and ANA gave a negative results. Urinalysis showed that the pH was 5.0 with protein levels of +3, leukocyte of +2, erythrocyte of +1 and a negative result for glucose. Microscope analysis of urine sediment showed 4-5 leukocyte cells per high power field, and was negative for erythrocytes and cylinders.

The patient was diagnosed as suffering from JRA and acute tonsilopharyngitis, with a differential diagnosis of systemic lupus erythematosus (SLE). The patient was treated with ibuprofen (30 mg/kg/day), divided into three equal doses, ampicillin injection (100 mg/kg/day, four times a day), and antacid syrup. The patient was also examined by the Ophthalmology Department and revealed that signs of uveitis were not found.

On the second day of admission, the temperature of the subject started to rise and during follow up a highly fluctuating fever was present. On the tenth day of admission, the subject complained of pain in the sternum. The respiratory rate was 48 times per minute and nasal flare was observed, but on chest inspection, no asymmetrical chest movement was seen. However, vesicular respiratory sound was decreased on the left side of the chest and was accompanied by fine rales and reduced vocal fremitus on the same side. No wheezing was heard. The heartbeat was normal and it was palpable at the fourth intercostal space in the left mid-clavicular line. On auscultation, the first and second heart sound was normal, and no murmur was heard. A chest X-ray revealed a pulmonary edema in the left lung (**Figure 1A**). The X-rays were repeated one day later (**Figure 1B**) and showed that the pulmonary edema had decreased, but that pleuropneumonia and cardiomegaly could be detected.

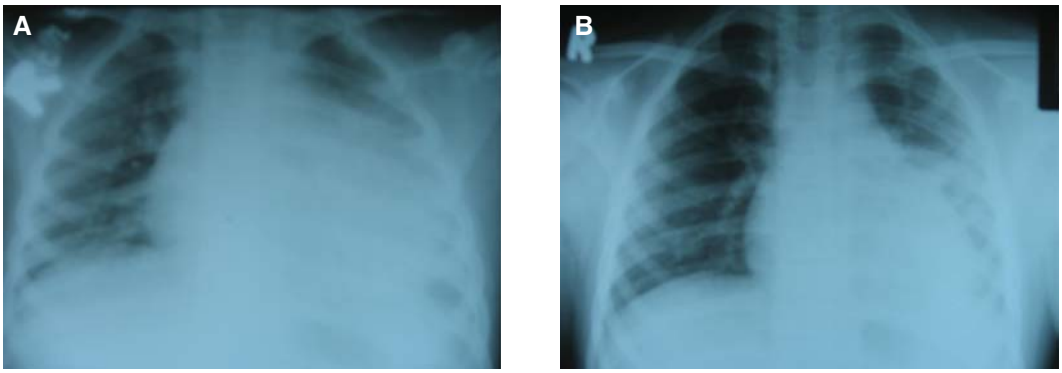

Figure 1. (A) Chest X-ray showing a pulmonary edema in the left lung. (B) Chest X-ray taken one day after (A) showing decreased of edema as well as pleuropneumonia and cardiomegaly.

On consultation, the Respirology Division suggested cefotaxime injections (1 gram every 8 hours). Examination of the subject by the Cardiology Division revealed a normal electrocardiogram and an echocardiograph showed minimal pericardial effusion. Suggested management was intravenous furosemide (30 mg every 12 hours), intravenous dexamethasone (5 mg every 8 hours) with no need for fluid restriction.

Based on these findings, the patient was diagnosed with systemic onset JRA (SoJRA). After cessation of intravenous dexamethasone, the patient was treated with oral prednisone (2 mg/kg/day given as 20 mg three times a day) and ibuprofen (30 mg/kg/day, given as 1 ½ teaspoons of Proris® syrup three times a day) for six weeks. The patient was managed with ambulatory (outpatient) care. We also ensured that adequate rest was taken during signs of inflammation, but also started to reintroduce activity gradually to achieve a normal life. In addition, education of the subject's family was also carried out to increase compliance to therapy and maintain daily needs for nutrition, activity and care.

We have also referred the subject for physiotherapy to prevent growth deformities. Since there has been contracture in the ankle joints caused by previous disease, subject also needs physiotherapy and medial wedge(s) and boot(s).

On subsequence observation during ambulatory care, it was found that some limitations to the small joints of the hands and wrists had occurred. For this condition, the subject is managed with occupational therapy. The problems with the knee and ankle joints were managed with short wave diathermy.

Table 1. Criteria for the diagnosis classification of juvenile rheumatoid arthritis[7]

1. Age of onset <16 years
2. Arthritis in one or more joints defined as swelling or effusion, or presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased heat
3. Duration of disease less than six weeks
4. Type of onset of disease during the first 6 months classified as:
   a. Polyarthritis: five or more joints
   b. Oligoarthritis: four or fewer joints
   c. Systemic disease: arthritis with intermittent fever >103°F (39.5^{0}C)
   d. Psoriatic arthritis
   e. Spondyloarthropathy
5. All other diseases must be excluded.

Discussion

Diagnosis of JRA rests on several criteria: onset of disease during childhood, presence of chronic arthritis, and exclusion of a number of other diseases. The period of childhood is usually considered as being before the 16th birthday. The presence of objective arthritis is necessary for diagnosis. Signs of objective arthritis include joint swelling and pain, in conjunction with loss of motion, warmth, or erythema. Joint pain alone with no other objective findings is properly called arthralgia rather than arthritis, and is not sufficient for a diagnosis of JRA. Chronicity is an important diagnostic consideration. According to official guidelines, arthritis must be present for six consecutive weeks before a diagnosis of JRA can be made.[6] Childhood arthritis can present insidiously in 1-4 joints (oligoarticular) or many joints (polyarticular) or with abrupt sudden painful swelling. Some patients (with systemic onset) will present with a high spiking fever, rash, hepatosplenomegaly, and lymphadenopathy for weeks to months before arthritis develops. Children with oligoarticular arthritis are well and usually have little pain. All children with potential arthritis have infection and malignancy in their differential diagnosis.[6-8]

Diagnosis and classification of JRA are based on American Rheumatism Association (ARA) criteria (see **Table 1**).

In our case, the diagnosis JRA was established by the ARA criteria. The subject was 11 years old and had been suffering from arthritis for four years. The joint pain was accompanied by redness, swelling, and a warm sensation and he was not able to walk by himself. The joints involved were the ankles, wrists, knees and fingers (the inter phalanx joints). There was also joint stiffness in the morning that decreased in the afternoon. Each episode of the disease lasted about two months.

Diagnosis of SoJRA is often challenging, especially if children have not had symptoms for six weeks. Infectious diseases and other inflammatory conditions may mimic SoJRA. Systemic-onset JRA affects about 10% to 20% of all patients who have

JRA. There is a slight male preponderance. The disease may present at any age during childhood and occasionally presents during adulthood. Extraarticular manifestations of SoJRA are high intermittent fever, rheumatoid rash, hepatomegaly, mild hepatic dysfunction, splenomegaly, lymphadenopathy, pleuritis, pericarditis (rarely myocarditis), abdominal pain, leukocytosis, severe anemia and Disseminated Intravascular Coagulation Syndrome.[2,6,8] In our case, the diagnosis of SoJRA was established using the ARA criteria by history and observation. Extraarticular manifestations were pulmonary edema and pericardial effusion, and high fluctuating fever.

A number of conditions can be confused with JRA and must be considered and excluded before making the diagnosis of JRA. Usually, a careful history and physical examination, coupled with awareness of the diagnosis possibilities, will suffice. Potential differential diagnoses are infection (osteomyelitis, septic arthritis), malignancy (leukemia), other rheumatic diseases (SLE, vasculitis).[6,7] In our case**,** the differential diagnosis was SLE because that disease often begins with arthritis,; therefore long term observation must be done. Infection was less likely, since it usually affects a single joint. Malignancy could also be excluded because in malignancy, bone pain is usually more prominent than joint pain.

Pleuritis and pericarditis occur in about 50% of patients, although these complications generally are mild and may be entirely asymptomatic. When symptoms do occur, they include chest pain and dyspnea (discomfort during breathing). Rarely, severe pericarditis or even myocarditis occurs.[6] Miller *et al*[9] found three children with myocarditis as a part of JRA. The diagnosis was established by the appearance of cardiomegaly, or congestive heart failure, or both, in the absence of substantial pericardial effusion or extra cardiac. Treatment with a high dose of corticosteroid had been successful in rapidly controlling the acute phase. In our case, chest X-ray showed pulmonary edema and echocardiography investigation showed minimal pericardial effusion at the posterior wall of the left ventricle.

Chronic uveitis is an important and sometimes devastating complication of JRA although the early signs and symptoms may be minimal. This intraocular inflammation primarily affects the iris and ciliary body (iridocyclitis), but choroids may also be involved. The frequency varies from 2-34% in children with JRA[10] and a study by Schaller *et al*[11] diagnosed 8 of 70 children with JRA as having developed iridocyclitis. Potentially, iridocyclitis is a major cause of disability in JRA patients. This complication occurs more frequently in cases of monoarticular and pauciarticular JRA than in polyarticular JRA. In our case, uveitis was not found.

As there are no specific or diagnostic laboratory tests for JRA, the disease cannot be diagnosed or confirmed in this way. However, laboratory results may be useful to exclude other critical diagnoses (e.g., infection or malignancy).[6,7] Acute phase reactants such as the ESR and CRP generally are elevated and present during periods of inflammation, but none of these tests is diagnostic, and a number of children have normal ESR rates even during periods of active disease. CRP is a good marker of disease activity in systemic onset juvenile arthritis and can be followed as an indicator of treatment success. ESR may be normal in oligoarthritis and polyarticular arthritis, but is usually very high (>60 mm/hour) in systemic onset disease.[6,7] In our case, CRP was high but ESR was normal.

The measurement of RF is an important marker for assessing and monitoring immunologic response. Many rheumatic conditions and other chronic inflammatory processes may produce RF. The RF detected by standard laboratory testing is an IgM antibody directed against the Fc (crystallizable fragment) portion of IgG.[12,13] The "classic" RF associated with adult onset rheumatoid arthritis is found only in a small subgroup of children who have RF-positive polyarthritis.[6]

The ANAs are a family of antibodies that reacts with various nuclear constituents from human or other mammalian cells. ANAs are associated with systemic lupus erythematosus, but they also occur in a number of children who have JRA, most frequently those who have young onset pauciarticular disease but also in some who have seronegative polyarthritis and seropositive disease. They are strongly associated with early childhood-onset pauciarticular JRA and with the occurrence of chronic iridocyclitis.[6] ANA is almost never positive in children with systemic onset JRA.[1,7] In our case, RF and ANA were negative, supporting the seronegativity for SoJRA.

A number of considerations are important in designing therapy for children who have JRA. These include identification of the particular disease manifestations, understanding of the natural history of JRA and its manifestations, recognition of the overall prognosis, and awareness of the special burden that chronic illness places on children, adolescents, and their families. Effective management of children with juvenile arthritis involves multiple components including medical management; family-centered, community-based, coordinated care; psychosocial management; musculoskeletal rehabilitation; well-child health issues; and continuity of care. Medications including intraarticular long-acting steroids, non-steroidal anti-inflammatory drugs (NSAIDs), both traditional and COX-2 inhibitors), sulfasalazine, hydroxychloroquine, methotrexate, corticosteroids, anti-TNF (tumor necrosis factor) agents (e.g. etanercept, infliximab, adalimumab), and anti-IL-1 (interleukin 1) agents.[2,3,6,7]

Physical and occupational therapy include a home exercise program, weekly to monthly therapy sessions, inpatient hospital treatment, shoe splints, joint protection, local heat, paraffin baths, a fluidotherapy pool program, and therapy coordination with a school therapy program.[7]

While it is important to appropriately manage the medical aspects of arthritis in children, it is important to provide psychosocial interventions such as: patient/family education, psychosocial interventions/support services, community resources, school based resources, information and referral regarding insurance coverage and benefit coordination.[7]

The medical therapy for systemic manifestations of SoJRA includes steroid and non steroid agents.[6] Systemic manifestations generally persist for fewer than six consecutive months, and steroid therapy should rarely exceed this time period. Corticosteroids usually are effective in initial doses of 1 to 2 mg of prednisone per kilogram of body weight. The dose can be tapered under a cover of non steroidal therapy as soon as fever and other manifestations have been suppressed. Administration of corticosteroids in doses large enough to cause cushingoid side effects should be avoided.[2,3,6,7] **Figure 4** shows an algorithm for medical treatment of systemic arthritis in JRA.[3] In our case, we combined a NSAID (ibuprofen) and steroid treatment (beginning with intravenous dexamethasone and followed by oral prednisone for six weeks). We used an algorithm proposed by Hashkes *et al*[3] for polyarthritic JRA to manage arthritis in systemic JRA.

The prognosis of this disease is highly variable. There are some differences in the outcome according to subgroup of disease but, overall, 75 - 80% of children can be expected to survive JRA without serious disability. Systemic-onset JRA, although a serious illness, is rarely fatal, particularly since the advent of modern drug therapy. Children at greatest risk for joint destruction appear to be those who have systemic-onset disease and those who have RF-positive polyarthritis.[6] Poor prognostic indicators for patient with JRA were active systemic disease at 6 months, polyarticular onset or disease course, female gender, increased RF level, persistent morning stiffness, tenosynovitis, subcutaneous nodules, presence of ANAs, early involvement of small joints in hands and feet, rapid appearance of erosions, and extended pauciarticular disease course.[2,14,15]

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