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Case Report FAMILY MEDICINE

Systemic juvenile idiopathic arthritis as a fever of unknown origin

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is a rare inflammation with still unidentified cause. It can also be cause of fever of unknown origin. Diagnosis is made by eliminating infection, malignancy, and rheumatological diseases. In this report, case of a 5-year-old patient with symptoms of intermittent fever, areas of rash on the body, itching, and swelling, redness, and pain in the right and left ankle is described. Serological test results were negative for infectious agents, and malignancy was excluded. Patient was diagnosed with systemic JIA associated with intermittent fever, negative rheumatological markers and negative serology test results. Treatment with methylprednisolone and methotrexate yielded positive clinical response. Diagnosis of systemic JIA can be challenging, and must be made by eliminating other diseases.

Keywords: Arthritis; cause of fever of an unknown orgin; systemic JIA.

Systemic JIA is a rarely seen inflammatory disease of unknown etiology characterized by high fever and extraarticular findings. Diagnosis is made by eliminating malignancy and other rheumatological diseases [1].

Incidence of systemic JIA varies from country to country [2, 3]. Average incidence and prevalence rates detected range between 0.92 to 2.5/100.000 and 1.2 to 11.3/100.000, respectively. Systemic JIA has no pathognomonic sign; diagnosis is made by ruling out etiological factors such as collagenous tissue disease and infection. Though its etiopathogenesis is not precisely known, 2 primary etiologies have been emphasized: immunological predisposition and environmental factors. Among environmental influences, infection is most frequently thought to be significant, but stress and trauma are also considered to have important roles in etiology [1].

Presently described is case of a 5 year-old patient with symptoms including swelling, redness and pain in the right and left ankles. Following tests and clinical follow-up, patient was diagnosed as systemic JIA.

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CASE REPORT

A 5-year-old female child was brought to outpatient clinic with complaints of rash and itching on her body, and swelling, redness, and pain in both ankles. Detailed anamnesis revealed that itching and redness on her elbows and knees had appeared 3 weeks earlier and she had received treatment for allergy at another medical facility. For 3 weeks she had periods of fever, during which rash had spread all over her body. Right and left ankles then became red and swollen. The patient was admitted to investigate etiology of fever of unknown origin. Vital signs were: body temperature, 36.5°C; pulse rate, 80/bpm; respiratory rate, 17/min; arterial blood pressure, 90/60 mmHg. On physical examination, rash and swelling on both ankles and maculopapullary skin eruptions all over the body, and particularly on extremities, were observed (Figure 1).

Biochemical parameters of the patient included: white blood cell count (WBC), 10.8x10^3/uL; hemoglobin (Hb), 9.8 gr/dL; platelets, 521x103/uL; aspartate transaminase, 21 U/L; alanine transaminase, 8 U/L; erythrocyte sedimentation rate (ESR), 103 mm/h; C-reactive protein (CRP), 7.82 mg/dL (<0.5); ferritin, 382 ng/mL; fibrinogen, 644.92 mg/dL (200–400); D-dimer, 1.88 mg/mL (0–0.5); and prothrombin time, 14.7 s (11–14). To rule out malignancy, bone marrow aspiration was performed. Malignancy was not detected, and histopathology was reported as infection or collagenase. No pathogenetic agent was detected in urine or blood cultures. Serological tests yielded negative results for mycoplasm, chlamydia, toxoplasm, rubella, and collagen tissue disease markers (anti-double strand DNA, anti-smooth muscle antibody, anti-mitochondrial antibody, anti-Sjogren's syndrome A and B, and anti-Sm antibody). Rheumatoid factor (RF) was 9.94 IU/mL (<19). Following all tests, diagnosis of juvenile idiopathic arthritis was made based on consideration of available anamnesis and clinical and laboratory findings. Steroid treatment at daily dose of 30 mg/kg was initiated. After 3 days of pulsed methylprednisolone treatment, steroid maintenance treatment (methylprednisolone) at daily dose of 2 mg/kg was initiated. The patient did not experience febrile episode after initiation of steroid therapy. On sixth day of treatment, painful rash appeared on right and left ankles. Methotrexate at dose of 10 mg/m^2 was added to the treatment. On 10th day, some notable hematological parameters were as follows: Hb, 10 gr/dL; platelet count, 713x10^3/uL; CRP, 1.61; and ferritin 51 ng/mL. Biochemical parameters were within normal limits. On 14th day of treatment, her body temperature rose and her state of general health deteriorated. CRP level increased to 6.78 mg/dL. Pulsed steroid (methylprednisolone) treatment at daily dose of 30 mg/kg was repeated for 3 more days followed by maintenance treatment at daily dose of 2 mg/kg. During follow-up, CRP was measured at 0.33 mg/dL, and ESR regressed to 20 mm/hr. General state of the patient improved and she was discharged, with treatment to be maintained on ambulatory basis. At third month, treatment of 8 mg/d methylprednisolone and methotrexate at weekly dose of 10 mg/m^2 continued.

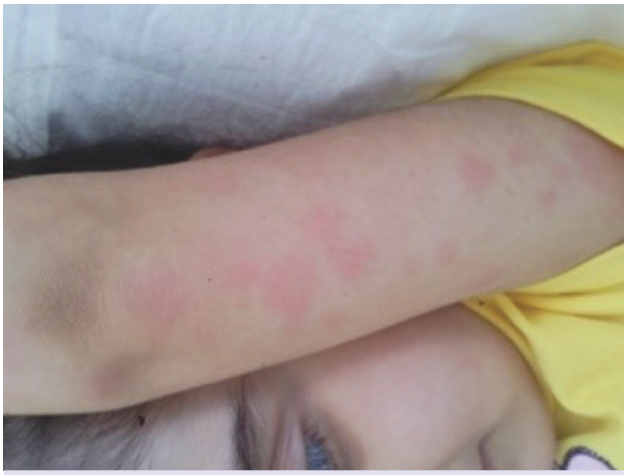

Figure 1. Rash was observed on upper extremity of the patient.

DISCUSSION

In developed countries, 10% to 20% of patients with JIA develop systemic JIA; in our country, it is the largest JIA subgroup. It is characterized by intermittent high fever and other extraarticular symptoms. No gender difference has been reported. Although children may be affected at any age, generally they are younger than 4 years of age. Characteristic feature is fever of up to 39.5°C occurring once or twice a day before returning to normal or even below normal level [4]. In these patients, as was the

case with our patient, temperature frequently peaks once in the morning and once at night. In most patients, pink-colored, occasionally itchy, and typically macular eruptions with pale center measuring less than 1 cm appear on the body, most often on the trunk and proximal part of the extremities, and then spontaneously resolve with drop in body temperature [4]. Rash may lead to misdiagnosis of allergy. Febrile peaks may not be typical at onset of disease and may occur after onset of treatment. In our patient, interval between onset of fever and establishment of diagnosis of systemic JIA was approximately 3 weeks, during which time fever was not under control and was therefore evaluated as fever of unknown origin [4].

Other systemic findings include fatigue, somnolence, irritability, and muscle pain. These symptoms are generally seen during episodes of fever and resolve with decrease in body temperature. In many patients, marked myalgia, arthralgia, or transient arthritis may be seen, especially during febrile episodes. These signs also regress with drop in body temperature [5]. As in present case, most often knee, elbow, ankle, wrist, or hip joints are affected; however, any small joint may be involved [4, 5]. Occasionally, the disease can recur as attacks without any clinical manifestation (fever, rash) apart from systemic symptoms. Less frequently, the disease can include tenosynovitis, synovial cyst, peritonitis, valvulitis with or without myocarditis, pulmonary parenchymal disease, central nervous system or renal involvement, stridor due to involvement of cricoarytenoid joint, or lymphedema. In nearly one-third of patients, significant lymphadenopathy and/or hepatosplenomegaly is seen [4]. In our patient, lymphadenopathy and hepatosplenomegaly were not detected. Depending on the inflammatory process, mild increase in hepatic enzymes may occur during active period of the disease. In nearly 50% of the patients with pleurisy, and especially those with pericarditis, level of hepatic enzymes is increased. However, most patients are asymptomatic. Pericarditis and myocarditis respond very rapidly to steroid treatment. Arthritis may accompany these symptoms or manifest weeks or months later and may complicate diagnosis [6, 7]. In patients with systemic JIA, marked leukocytosis with left shift may be seen. WBC count may exceed 100.000/mm^3 [4]. In our patient, count was 10.800/mm^3. As was the case with presently described patient, elevation of CRP, ferritin, C3, and C4 levels, and pronounced normocytic-normochromic or microcytic-hypochromic chronic anemia may be present. In 40% of patients, significant anemia is seen. Anemia may be related to iron deficiency, inadequate nutrition, or gastrointestinal loses due to medications [6]. In almost all cases of systemic-onset JIA, anti-nuclear antibody and RF are negative [4, 7]. ESR increases markedly, and in most cases, exceeds 100 mm/h. Consumptive coagulopathy and serious deterioration of hepatic functions may be seen. Ferritin level, which is acute phase marker, may increase significantly. Increased sedimentation rate with other signs of chronic inflammation, and normal or low platelet count should suggest alternative diagnosis (leukemia, sepsis) or JIA complicated by consumptive coagulopathy. Moderate degree of coagulopathy is frequently observed in patients with systemic arthritis. In small number of patients, macrophage activation syndrome (MAS), or hemophagocytic syndrome, may develop. MAS is a life-threatening disease [1, 6]. It has also been reported in patients with polyarthritis, and it has been suggested that development may be due to use of nonsteroidal anti-inflammatory drugs (NSAIDs), intramuscular gold preparations, or sulphasalazine. Patient need not be in typical systemic-onset period for MAS to be observed. These patients' symptoms include chronic fever, hepatosplenomegaly, lymphadenopathy, and encephalopathy. Definitive diagnosis is made based on bone marrow aspiration findings and demonstration of hemophagocytosis in tissue cultures [6, 7].

Generally, uveitis is not seen in patients with systemic JIA. Secondary AA-type amyloidosis is an important potential complication of the disease. Although it is rarely seen in the USA, it is reportedly observed in 5% of patients in Europe [1]. As indicated in a study conducted by Ozdogan et al., in our country, incidence of uveitis decreased from 10% to 5% due to greater use of therapeutic agents and closer monitoring of patients [8].

In our case, inability to detect any etiological agent in serological or microbiological examination, negative collagenous tissue markers, exclusion of malignancy, and finally, response elicited by steroid

therapy established diagnosis of systemic JIA.

Previously, pyramid approach had been recommended in treatment planning. As first-line treatment, aspirin or NSAIDs were used, followed months later by antimalarials, gold salts, or D-penicillamine [4]. Now, however, this treatment approach has been abandoned.

Current treatment strategy inverts previous pyramid:

- Corticosteroid treatment 1–2 mg/kg/d
- Intense, high dose steroid (30 mg/kg/dose)
- Methotrexate (10–20 mg/m^2/wk)
- If increased dose does not generate treatment response, then etanercept and infliximab are added to treatment [1].

In conclusion, though rarely seen, systemic JIA is an important disease to be considered in patients who present with fever of unknown origin, multisystem involvement, and joint complaints, in particular. Better understanding of this disease will enable us to detect new cases more easily.

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REFERENCES

1. Petyy RE, Cassidy JT, Chronic arthritis. In: Cassidy JT, Petty RE. editors. Textbook of Pediatrik Rheumatology. 5th ed. Elsevier Saunders; 2005: p. 206–341.
2. Fink CW, Fernandez-Vina M, Stastny P. Clinical and genetic evidence that juvenile arthritis is not a single disease. Pediatr Clin North Am 1995;42:1155–69.
3. Graham TB, Glass DN. Juvenile rheumatoid arthritis: ethnic differences in diagnostic types. J Rheumatol 1997;24:1677–9.
4. Neyzi O, Ertuğrul T. Pediatri. 2. Baskı. Nobel Tıp Kitabevleri: İstanbul; 1993. s. 329–35.
5. Isenberg D, Maddison P, Woo P, Glass D, Breedveld F. editors. Oxford Textbook of Rheumatology. 3th ed. Oxford University Press: London; 2004.
6. Woo P, Laxer RM, Shery DD. Klinik Uygulamada Pediyatrik Romatoloji. Kasapçopur Ö. çeviri ed. Deomed Yayıncılık: İstanbul; 2009.
7. Kasapçopur Ö, Özdoğan H. Jüvenil idyopatik artrit. Türkiye Klinikleri J Pediatr Sci 2008;4:31–42
8. Ozdogan H, Kasapçopur O, Dede H, Arisoy N, Beceren T, Yurdakul S, et al. Juvenile chronic arthritis in a Turkish population. Clin Exp Rheumatol 1991;9:431–5.