Case Report / *Olgu Sunumu*

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Is it Atypical Kawasaki Disease or Evolving Systemic JIA?

Atipik Kawasaki mi? Yoksa Gelişmekte Olan Sistemik JIA mı?

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Abstract

Coronary arterial dilatation (CAD) may be a rare cardiac manifestation of systemic juvenile idiopathic arthritis (sJIA). Patients with prolonged fever and CAD may be initially misdiagnosed as incomplete Kawasaki disease. An eight-year-old boy complained of fever that typically rose with chills every 24 hours, particularly at night, with a maximum of 39.5 °C, lasting for 17 days. Physical examination did not reveal any abnormalities, but laboratory tests showed increased acute phase reactants and neutrophilic leukocytosis. The infectious work-up was normal. After echocardiographic examination showed CAD, the boy was treated with intravenous immunoglobulin (IVIG). However, the fever persisted, and the clinical picture changed into macrophage activation syndrome, leading to a final diagnosis of sJIA, leading us to make the final diagnosis as sJIA. CAD may rarely be the initial sign of sJIA. The suboptimal response to IVIG therapy may be a clue for diagnosis.

Keywords: Coronary arterial dilatation, Kawasaki disease, systemic juvenile idiopathic arthritis.

Öz

Koroner arter dilatasyonu (KAD), sistemik juvenil idiyopatik artritin (sJIA) nadir görülen kardiyak belirtilerinden biri olabilir. Uzun süreli ateş ve KAD'si olan hastalara başlangıçta inkomplet Kawasaki hastalığı olarak yanlış tanı konulabilir. Sekiz yaşında erkek hasta, özellikle geceleri, genellikle 24 saatte bir titremeyle yükselen, en fazla 39.5 °C'ye ulaşan ve 17 gündür devam eden ateş şikayetiyle kliniğimize başvurdu. Fizik muayenede herhangi bir patoloji saptanmadı. Laboratuvar incelemelerinde belirgin akut faz yanıtı artışı ve nötrofilik lökositoz tespit edildi. Enfeksiyon etiyolojisine yönelik yapılan tetkikler normaldi. Ekokardiyografik incelemede KAD saptanan hastaya intravenöz immünoglobulin tedavisi uygulandı. Ancak ateşi devam eden hastada klinik tablo makrofaj aktivasyon sendromuna dönüştü. Bu gelişmeler sonucunda hastaya nihai olarak sJIA tanısı konuldu. Koroner arter dilatasyonu, nadiren sJIA'nın ilk belirtisi olabilir. İntravenöz immünoglobulin tedavisine verilen suboptimal yanıt, ayırıcı tanıda bir ipucu olabilir.

Anahtar Kelimeler: Koroner arter genişlemesi, Kawasaki hastalığı, sistemik juvenil idiyopatik artrit

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is characterized by prolonged fever, rash, and arthritis. It affects children under the age of 16 years and accounts for approximately 10 to 20% of all JIA cases (1). Hepatosplenomegaly, lymphadenopathy, serositis, neutrophilic leukocytosis, and increased acute phase reactants are the other prominent features. Specific symptoms of the disease, including rash and joint pain, may not always be apparent at the time of presentation, rendering a diagnosis

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problematic in some instances (2). Since various infectious or malignant diseases may cause a similar clinical picture, sJIA diagnosis is often made by excluding other causes.

Pericardial effusion is the most common cardiac manifestation of sJIA (1). In some individuals, echocardiographic evaluation may detect coronary artery dilatation (CAD), which is similar to Kawasaki disease (KD) (3). Therefore, patients with prolonged fever and CAD may be misdiagnosed as incomplete KD (4). The diagnosis of sJIA is often made by a lack of response to intravenous immuneoglobulin (IVIG) therapy and the emergence of other disease-specific findings. Herein, it was aimed to report an evolving sJIA case that had been previously thought to have incomplete KD.

Case Report

An eight-year-old Kazakh male patient presented with a complaint of fever lasting for 17 days. He had previously been hospitalized in Kazakhstan for ten days and given antibiotics. Then, he was brought to our clinic since his fever persisted. From his history, it was learned that he was healthy before, his vaccinations were done following the Kazakhstan Ministry of Health program, there was no risk factor for brucella, no contact with ticks and animals, and no history of tuberculosis (TB) in the patient or family.

At admission, his body temperature was 36 °C, heart rate was= 70/min, respiratory rate was= 18/min, blood pressure= 120/69, and oxygen saturation was= 97%. There was no pathological finding in his physical examination, his cardiological examination was normal, and there was no rash, hepatosplenomegaly, or lymphadenopathy.

Initial laboratory analysis revealed neutrophilic leukocytosis and increased acute phase reactants (Table 1). There were no atypical lymphocytes in the peripheral blood smear.

He was started on broad-spectrum antibiotics (teicoplanin+piperacillin-tazobactam) covering nosocomial pathogens after blood cultures were taken. The patient's fever typically rose with chills every 24 hours (particularly at night), with a maximum of 39.5 °C. Neither arthralgia nor rash was accompanying fever. Detailed serological examination, including human immune deficiency virus, Epstein-barr virus, cytomegalovirus, toxoplasma, brucella, salmonella, *Borrelia burgdorferi*, leptospira, parvovirus, which was requested for the etiology of prolonged fever, was negative. Nasopharyngeal multiplex real-time polymerase chain analysis test searching 20 common respiratory pathogens (including adenovirus, influenza virus, and coronaviruses) in addition to four bacteria (*Bordetella pertussis, Bordetella parapertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae*) were negative.

Regarding TB, interferon-gamma release assay was negative, and chest X-ray was normal. The analysis of thick blood smears for malaria was also negative. No pathology was detected in abdominal ultrasonography. Cranial and abdominal magnetic resonance image that had been performed in his country was reevaluated and reported to be normal.

Table 1. Laboratory summary of the patient during follow-up

Value	Normal Values	First Admission	4th Day	8th Day	Second Admission	6th Day of Second Admission	Last Visit (1st month)
Hemoglobin (g/dL)	11.5-14.5	10.6	9.8	10.5	11.6	9.9	10.2
White blood cell count (10^3/uL)	4.5-13.5	15.700	34650	16980	19660	3200	9800
Neutrophiles (10^3/uL)	1.4-6.4	12.110	32030	14000	15860	1490	8510
Lymphocytes (10^3/uL)	1.5-7	2720	1860	1980	1960	980	800
Platelets (10^3/uL)	150-400	442.000	381000	444000	198000	184000	344000
Creatinine (mg/dL)	0.4-0.6	0.32	0.51	0.43	0.48	0.31	0.4
Alanine amino transferase (U/L)	<44	10	9	10	165	184	36
Aspartate amino transferase (U/L)	<55	14	19	14	119	38	17
Ferritin (ng/mL)	20-200	309.3	595		17222	1837	154.6
Erythrocyte sedimentation rate (mm/sa)	<15	59			41	5	
Fibrinogen (mg/dL)	199-409	309.3	560		507	128	338
C-reactive protein (mg/L)	<2.8	29.6	69.6	22.4	103.6	4.2	<1
Troponin-I (ng/mL)	<0.16	<0.1					
Tryglyceride(mg/dL)	30-100		53		383		
Treatment		Teicoplanin +piperacillin-tazobactam	IVIG (2g/kg over 12 hrs) +aspirin (50 mg/kg/d)	IV MP (2 mg/kg/d; max 60mg/d)* Was initiated 36 hours after IVIG.	Pulse MP (30 mg/kg/dose; maximum 1 gr/d IV) +oral cyclosporine (5 mg/kg/day)	IV MP (2 mg/kg/d; max 60mg/d)* +oral cyclosporine (5 mg/kg/day)	Oral cyclosporine (5 mg/kg/day)

IV: Intravenous, IVIG: Intravenous immunoglobulin, MP: methylprednisolone.

Bone marrow aspiration revealed hypercellular bone marrow with a hyperactive myeloid series and relatively hypoactive erythroid series. No atypical cells, storage cells, parasites, or hemophagocytosis were observed. Few plasma cells and a sufficient number of megakocytes were seen.

In the transthoracic echocardiography (ECHO) evaluation performed on the patient, the left coronary artery was= 4 mm (z score 1.6), and an increase in echogenicity was detected. The patient was given IVIG (2g/kg over 12 hrs) and aspirin (50 mg/kg/d) with the suspicion of incomplete KD. However, the patient's fever recurred 36 hours after IVIG, and C-reactive protein (CRP) and ferritin levels began to rise (Table 1). Intravenous methylprednisolone (MP) (2 mg/kg/d); max 60 mg/d) was initiated considering IVIG refractoriness. His fever suddenly dropped after the glucocorticoid (GC) treatment. His CRP level became normal levels. After five days of full-dose GCs, the MP dose was started to be tapered.

While the MP was at a dose of 0.4 mg/kg/g, the patient's fever began to rise again, and he experienced bilateral knee pain. However, the signs of arthritis were not present. His laboratory analysis revealed neutrophilic leukocytosis, increased transaminases, high lactate dehydrogenase levels, hypertriglyceridemia, and markedly increased CRP, procalcitonin, and ferritin levels (Table 1).

Based on the current clinical and laboratory findings, the patient was diagnosed with macrophage activation syndrome (MAS) secondary to sJIA. Pulse MP (30 mg/kg/dose; maximum 1 gr/d IV) and 5 mg/kg/day oral cyclosporine treatment was initiated. The patient's fever did not recur, and laboratory tests gradually returned normal. Control ECHO, performed on the sixth day, was normal. He is still being followed up in our outpatient clinic.

Discussion

Although cardinal features of sJIA include fever, arthritis, rash, and organomegaly, the full expression of the disease may not be present initially (1,4). Previous reports have highlighted that only 30% of the cases meet all diagnostic criteria at admission, and nearly 71% of sJIA patients will eventually express them during their illnesses (2,5). Therefore, diagnosis can be challenging and requires a high index of suspicion. Similarly, in our patient, the only prominent finding at first admission was the presence of a fever that had persisted for about three weeks. During follow-up, he had a daily spiking fever with chills rising to 39.5 °C. Vomiting was accompanied by fever almost all the time, and the body temperature became to normal limits after paracetamol application. We did not detect any rash. However, according to the family's statement, there was a rash during previous hospitalization in his country, but this was associated with the use of antibiotics by the clinicians. Although his physical examination was normal, and there was no sign of arthritis, he complained of bilateral knee pain during his second admission.

Laboratory examination revealed neutrophilic leukocytosis and increased acute phase reactants. A comprehensive work-up revealed no infectious or malignant cause. Since ECHO examination revealed CAD, we thought the patient may have incomplete KD, and we gave IVIG treatment. Some sJIA cases are initially diagnosed with atypical KD in the literature (3,4). In Dong S. et al.'s study, when 6745 patients diagnosed with KD were evaluated, it was discovered that 0.2% had sJIA (4). Besides, as in the present case, MAS was more common among these individuals, and they were predominantly from the Caucasian race (4). It enabled us to retrospectively diagnose evolving sJIA in our patient who experienced apparent MAS findings in the follow-up (6).

Response to IVIG treatment in sJIA patients is suboptimal, as in our case. Such a condition may be due to IVIG refractory incomplete KD or a rare presentation form of sJIA. Prolonged fever, clinical findings related to multi-organ involvement, rash, and coronary artery anomalies can also be seen in multisystem inflammatory syndrome in children (MIS-C). KD and MIS-C overlap clinical syndromes with often similar treatment options (7). In such cases, IVIG, GC, or biological agents may be preferred as mono or combination therapy, depending on the severity of the illness (8-10). Although coronavirus disease-related epidemiological association and/or laboratory confirmation were helpful in the diagnosis of MIS-C in the early period of the pandemic, diagnosis has become difficult today due to the high rate of positive serological tests in the general population. We also considered similar differential diagnoses in our case in the first place. Hence, we initiated high-dose aspirin together with IVIG. Although the time without fever was prolonged to 36 hours, the decrement in acute phase reactants was not prominent. Afterwards, considering the possibility of MIS-C, we administered MP at 2 mg/kg/day. The patient's response to GC treatment was dramatic. However, the patient's fever recurred when the MP dose was tapered. MAS, manifested by elevated transaminases, hypertriglyceridemia, low platelets, and increased ferritin in laboratory parameters, became evident.

sJIA is a clinical picture with a higher mortality rate than KD (4). MAS may occur in patients with a previous diagnosis of sJIA or sometimes as the first finding at the time of diagnosis (6). Therefore, it is necessary to make a rapid diagnosis and initiate appropriate treatment, including high-dose steroids, cyclosporine, and biological agents. For our patient, we started high-dose MP and cyclosporine therapy simultaneously. The fever did not recur after the first dose of pulse steroids. Laboratory values returned to normal limits in approximately ten days. Coronary arteries were evaluated as normal in the control ECHO examination.

In conclusion, coronary artery involvement may rarely be the initial sign of sJIA. The suboptimal response to IVIG therapy may be a clue for diagnosis.

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