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THE APPROACH TO INCOMPLETE KAWASAKI DISEASE IN INFANTS

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The manifestations of Kawasaki disease in infants are often subtle and many times infants with this condition do not meet full diagnostic criteria. The approach to incomplete Kawasaki disease remains a challenge for physicians because clinical features may be mistaken for symptoms of other conditions. Young infants are at an extremely high risk of developing coronary arterial abnormalities compared to older children, probably due to the delay in diagnosis and the fact that only a small number receive intravenous immunoglobulin (IVIG) during the first 10 days of illness. We present a 5-month-old boy treated at our pediatric intensive care unit. The boy presented with fever lasting for more than five days, unresponsive to antibiotic therapy, changes in extremities (erythema, edema and desquamation), polymorphous rash, changes in the lips and oral cavity, seizures, irritability, pyuria, anemia, leukocytosis and raised titer of acute phase reactants. The presence of rash was initially mistaken for a reaction to antibiotics administered for a presumed urinary tract infection. All bacterial cultures and serologic tests were negative. Echocardiography showed no abnormality, but according to the criteria for incomplete Kawasaki disease published by the American Academy of Pediatrics and American Heart Association, we decided to treat the child with IVIG. With this report, we would like to highlight the importance of a high degree of clinical suspicion of Kawasaki disease in infants in whom the presentation is often incomplete, while prompt IVIG therapy is crucial to avoid serious cardiac complications.

Descriptors: MUCOCUTANEOUS LYMPH NODE SYNDROME – diagnosis, immunology; INFANT

INTRODUCTION

Infants with Kawasaki disease (KD), particularly those younger than 6 months, may present with unexplained fever, or the fever may be accompanied by only two or three of the clinical features of classic KD (1-3). Atypical presentation of KD is recorded in 28% of infants as compared with 7%-10% of older children (4). Coronary artery dilatation develops in approximately one-third to one-half of patients and can be detected by echocardiography 12 to 24 days after the onset of symptoms. Coronary artery aneurysms develop in 15%-20% of affected patients (3, 5-7).

Cardiac sequelae are much more common in infants, particularly in the first 6 months, than in older children with KD, probably due to the delay in diagnosis and the fact that only a small number receive intravenous immunoglobulin (IVIG) during the first 10 days of illness (3, 4, 8). One previous study demonstrated 85% of infants younger than 6 months with incomplete KD and not treated with IVIG to have developed coronary artery aneurysm (4, 9). Coronary artery complications did not develop in any patient having received IVIG before echocardiographic evidence of such complications, regardless of age (4, 9).

IVIG therapy combined with a high dose of salicylate is known to prevent coronary artery complications if given before symptoms develop. With prompt therapy, this complication decreases to about 5% (3, 5, 8, 10). Thus, although being important for the diagnosis and follow-up, echocardiography is inadequate as a criterion for early treatment and a normal echocardiogram should not preclude treatment (8).

Since young infants with KD are at an extremely high risk of developing coronary arterial abnormalities, early diagnosis and appropriate therapy are very important (4).

With this case report, we would like to underline the importance of clinical suspicion of this disease in infants and the necessity of appropriate treatment as early as possible in order to avoid serious cardiac complications of the disease.

CASE REPORT

L. R., a 5-month-old boy, was admitted for fever up to 39.5°C, febrile seizures and diarrhea. It was the first day of illness. Physical examination revealed only extreme irritability. Initial laboratory findings revealed white blood count of 15800/mm^3, platelet count of 241000/mm^3, hemoglobin level of 105 g/L, erythrocyte sedimentation rate 78 mm/hour, normal cerebrospinal fluid; urinalysis: significant pyuria 40-50 WBC *per* high-power field, ALT normal, albumin >30 g/L. Based on these results, we decided to treat the child

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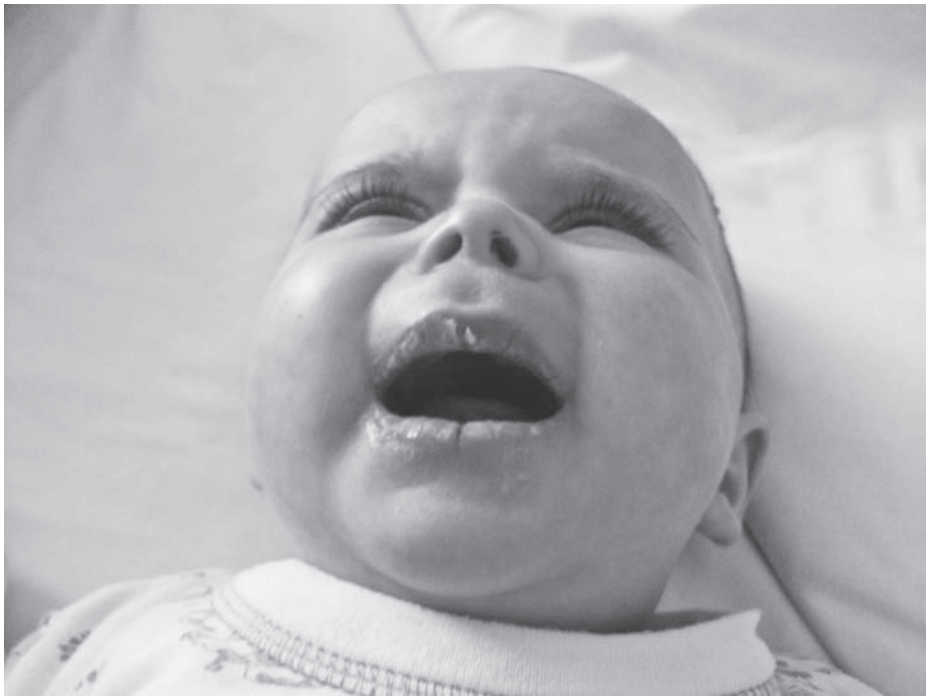

Figure 1. *Red, swollen and fissured lips*
Slika 1. *Crvena, otečena i ispucala usta*

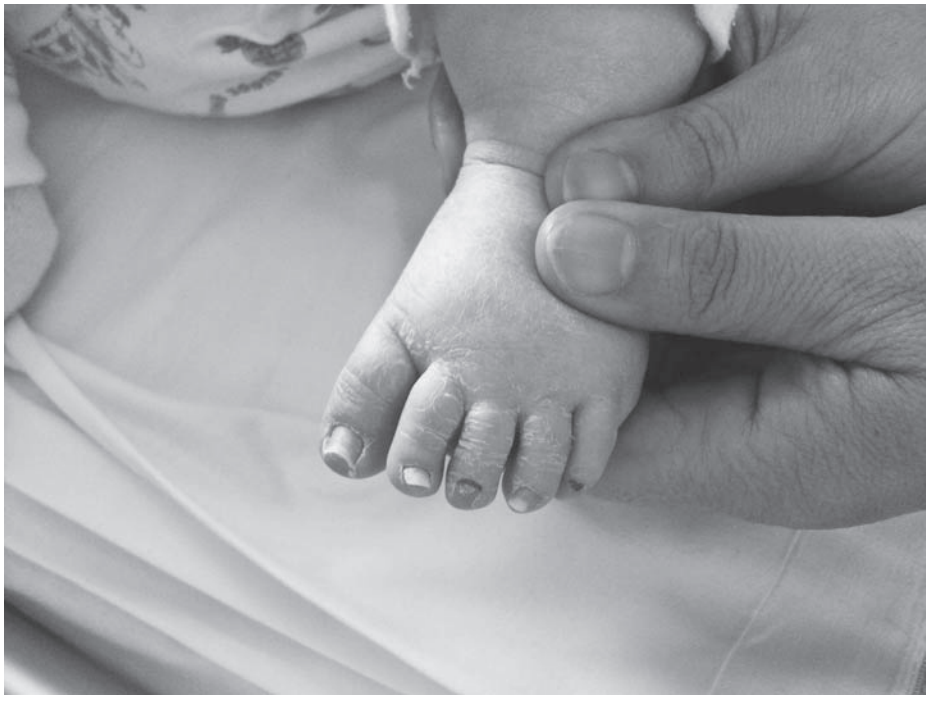

Figure 2. *Feet edema*
Slika 2. *Edem noge*

with cefazoline (i/v) for urinary infection (urine culture pending). Two days after the introduction of antibiotic therapy, the child presented a maculopapular rash. At first, it was considered to be a reaction to cefazolin and we decided to change therapy to cotrimoxazole + gentamicin, later changed to vancomycin + gentamicin. Despite all, the child's clinical condition aggravated. Fever remained at 39-40°C all the time. The rash persisted for 4-5 days. At the end of the first week of treatment, the child presented edema of the hands and feet, strawberry tongue, and red, swollen and fissured lips (Figures 1 and 2). All the time, he was quite irritable even when out of fever. After the first week, we found periungual desquamation (Figure 3).

All cultures (blood culture, urine culture, coproculture, cerebrospinal fluid culture and throat culture) showed negative results. The infant had received BCG vaccine. No reactivation of the scar was noticed. Serum titer for antistreptolysin O antibodies was normal. Results of serology for adenovirus, Epstein-Barr virus, measles, herpes virus, cytomegalovirus, Coxsackie viruses, HIV and *Rickettsia rickettsii* were negative.

C-reactive protein was 107 mg/L. Cardiac ultrasound revealed no abnormality. Despite normal echocardiogram, according to the criteria for incomplete KD published by the American Academy of Pediatrics and American Heart Association, we decided to treat the child with IVIG 2 g/kg/day and salicylic acid initially 100 mg/kg and later (three days after the child was afebrile) continued with 5 mg/kg for 8 weeks. Following IVIG administration, the child became afebrile. In two days, the hand and feet edema disappeared. The actual clinical condition of the child is very good, with normal echocardiogram on follow-up (9 months), normal C-reactive protein and erythrocyte sedimentation rate. Platelet count remained normal during the follow-up.

DISCUSSION

Kawasaki disease is a disease of unknown etiology, which generally affects children younger than 5 years, but is rare among infants younger than 6 months of age who account for 3%-11% of cases (1, 4, 6, 11).

The diagnosis of classic KD requires fever (>39°C) for more than 5 days and the presence of at least four of the following features: changes in extremities including erythema, edema and desquamation; nonexudative conjunctivitis; polymorphous rash (not vesicular); cervical lymphadenopathy, usually greater than 1.5 cm and unilateral; and changes in the lips and oral cavity (pharyngeal erythema, dry/fissured or swollen lips and strawberry tongue) (1, 2, 11). The manifestations of KD in infants are often subtle and many times infants with the condition do not meet full diagnostic criteria, as in our case. Particularly those younger than 6 months may present with unexplained fever only or the fever may be accompanied

by only two or three of the clinical features of KD (2, 12, 13).

In our patient, fever had persisted for more than 5 days and was unresponsive to antibiotic therapy, along with the following three clinical criteria: changes in extremities (erythema, edema and desquamation); polymorphous rash; and changes in the lips and oral cavity (Figures 1-3).

Infants have been found to differ from older children in several aspects. These differences are even more pronounced in infants with incomplete KD as compared with older children. The most common findings are rash and fever.

The approach to incomplete KD remains a challenge for physicians because clinical features may be mistaken for symptoms of other conditions (2). An infant with fever, rash and cerebrospinal fluid pleocytosis may be misdiagnosed with viral meningitis. Sterile pyuria may be mistaken for a partially treated urinary tract infection. The presence of rash is often mistaken for a reaction to antibiotics administered for presumed urinary tract infection, as in our case.

Infants have a high incidence of diarrhea, irritability and sterile pyuria, all of which were present in our case (8). In a review of incomplete KD, the authors report irritability in 64%, diarrhea in 29%, pyuria in 44%, respiratory symptoms in 47% and elevated aminotransferase level in 18% of cases (14).

According to literature reports, infants have a higher incidence of incomplete KD (45% *vs*. 12%) and coronary complications (64% *vs*. 9%) than older children (8, 15). Coronary artery complications developed in all of the infants with incomplete KD (8). In the Alberta Children Hospital in Canada, the incidence of coronary artery complications during a 10-year period was 14% with typical KD, 33% of infants with complete KD and 100% of infants with incomplete KD (8).

Patients developing coronary artery aneurysms were more likely to have their diagnosis established after 10 days of fever, due to a delay in recognizing KD by the physicians rather than a delay in seeking medical consultation by parents (16).

A questionnaire conducted by the University of California revealed that >50% of general pediatricians and 25% of infectious disease subspecialists did not consider the diagnosis of KD in children younger than 6 months and older than 8 years, while it is known that failure to consider the diagnosis at the extremes of the pediatric age range puts children at risk because coronary artery abnormalities occur more often in young infants and adolescents with KD (17, 18).

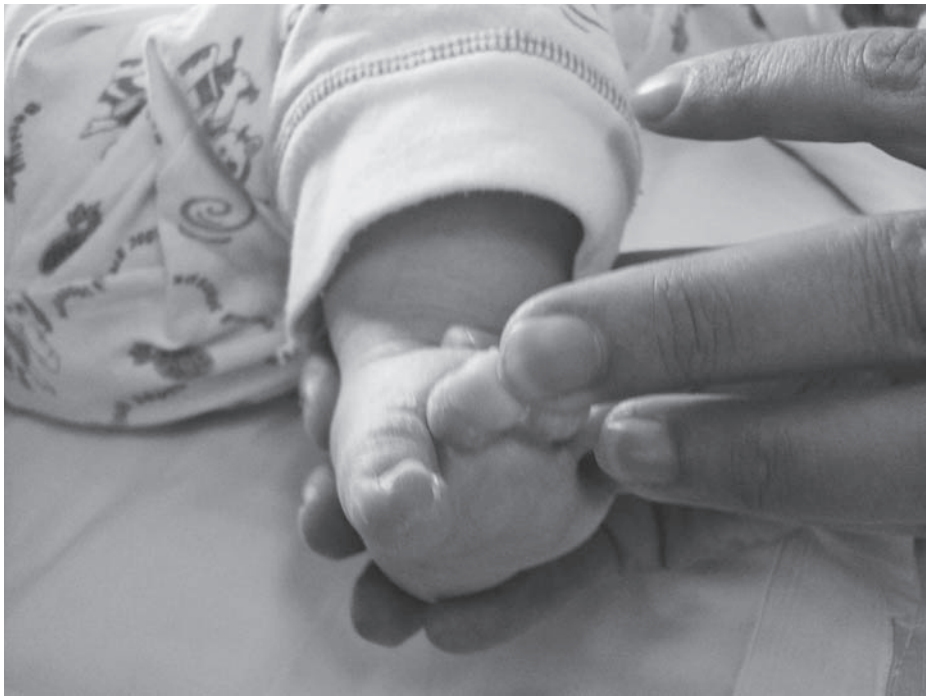

Figure 3. *Periungual desquamation*
Slika 3. *Periungvalna deskvamacija*

The incidence of KD is higher than previously reported, in part because earlier reports did not include incomplete forms (19). Many of the clinical features of KD may be present in other illnesses, therefore it is always necessary to rule out other diseases. Differential diagnosis should include the following:

- viral infections (e.g., measles, adenovirus, enterovirus, Epstein-Barr virus)
- scarlet fever
- staphylococcal scalded skin syndrome
- toxic shock syndrome
- bacterial cervical lymphadenitis
- drug hypersensitivity reactions
- Steven-Johnson syndrome
- juvenile arthritis
- Rocky Mountain spotted fever
- leptospirosis
- mercury hypersensitivity reaction

The new American Academy of Pediatrics/American Heart Association criteria (laboratory tests and early echocardiography) are helpful in the diagnosis of incomplete forms of KD (19). These criteria (3) enabled timely diagnosis and treatment of our patient. He had fever persisting for more than five days, three typical clinical features, elevated acute phase reactants and the presence of several additional laboratory results consistent with the diagnosis.

A review of literature reports reveals IVIG given within the first 10 days of the disease to reduce the risk of damage to coronary arteries of the heart in children (10). Therefore, physicians need to consider KD on differential diagnosis in children with prolonged fever without clear etiology (3, 20).

The rationale is that treatment is safe and effective and that failure to diagnose KD may have a significant unfavorable impact on outcome.

CONCLUSION

Physicians should keep a high clinical suspicion of KD in all infants with unexplained prolonged fever to prevent severe sequels. Intravenous immunoglobulin is known to be safe and its early use in infants with suspected incomplete KD is appropriate.

Authors declare no confilct of interest.
Autori izjavljuju da nisu bili u sukobu interesa.

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S a ž e t a k

PRISTUP NEPOTPUNOJ KAWASAKIJEVOJ BOLESTI U DOJENČADI

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Manifestacije Kawasakijeve bolesti u dojenčadi često su blage pa dojenčad s ovim stanjem ne ispunjava sve dijagnostičke kriterije. Pristup nepotpunoj Kawasakijevoj bolesti ostaje izazov za liječnike, jer se klinička obilježja mogu zamijeniti za simptome nekih drugih stanja. Rizik za razvoj nenormalnosti koronarnih arterija osobito je visok u mlađe dojenčadi u usporedbi sa starijom djecom, vjerojatno zbog zakašnjele dijagnoze te činjenice da ih tek manji broj primi intravenski imunoglobulin (IVIG) tijekom prvih deset dana bolesti. Prikazuje se slučaj 5-mjesečnog dječaka liječenog u našoj pedijatrijskoj jedinici intenzivnog liječenja. Dječak je dovezen u bolnicu s groznicom koja je trajala više od pet dana i nije reagirala na terapiju antibioticima, uz promjene ekstremiteta (eritem, edem i ljuštenje), polimorfni osip, promjene na usnicama i u usnoj šupljini, konvulzije, razdražljivost, piuriju, anemiju, leukocitozu i povišeni titar reaktanata akutne faze. Isprva je prisutnost osipa krivo protumačena kao reakcija na antibiotike koji su se djetetu davali zbog pretpostavljene infekcije mokraćnog sustava. Sve bakterijske kulture i serološke pretrage bile su negativne. Ehokardiografija nije pokazala nikakvu nenormalnost, ali smo prema objavljenim kriterijima za nepotpunu Kawasakijevu bolest Američke pedijatrijske akademije i Američkog udruženja za srce odlučili dijete liječiti pomoću IVIG. Ovim prikazom želimo naglasiti kako je važno ozbiljno posumnjati na Kawasakijevu bolest u dojenčadi kod koje je prezentacija ove bolesti često nepotpuna, a brzo uvođenje terapije IVIG bitno je kako bi se izbjegle ozbiljne srčane komplikacije.

Deskriptori: MUKOKUTANI SINDROM LIMFNIH ČVOROVA – dijagnoza, imunologija; DOJENČE

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