Evaluation of Roseola Infantum Cases in Terms of Demographic Properties and Laboratory Values*

Roseola İnfantum Olgularının Demografik ve Laboratuvar Değerleri Açısından Değerlendirilmesi

Zafer Bıçakçı[1], Muhammet Hafit Arvas[2], Canozan Biçer[2], Ahsen Akay[2], Sefer Üstebay[2], Döndü Ülker Üstebay[2]

[1] Pediatric Hematology Unit, Kafkas University School of Medicine, Kars, Turkey
[2] Department of Pediatric Health and Diseases, Kafkas University School of Medicine, Kars, Turkey

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Abstract

Objective: To share our experince from demographic and labaratory results of 46 patients who applied to our policlinic with complaints of fever and rash and diagnosed as roseola infantum between 2012-2016.

Material and Methods: Labaratory and demographic findings of 41 patients who diagnosed as roseola infantum clinically had been evaluated. Roseala infantum cases were diagnosed as 10 mo old infant with high temperature over three days and nontoxic maculopapuller rash on the trunk and after making differential diagnosis of other diseases that courses with skin rash and high body temperature. Neutrophil counts between 0-500, 500-1000 and 1000-1500 were accepted as high, medium and low, respectively.

Results: 25 of the patients were female (54.3%), 21 of them were male (45.7%), mean age was 11.5 ± 7.02 (3-36 months) and peak age of onset was 9-11 months. 76% of patients were (35/46) under one years of age. Disease was seen all year round but it was seen least at September and October and was seen mostly at December. Mean labaratory leves were found as: Hb 11.8 ± 0.97 g/L, HCT 35.0% ± 3.2, MCV 73.7 ± 5.10 fL, platelet count 299 ± 128.8 x 10⁹/L, leukocyte count 7.6 ± 2.8 x 10⁹/L, neutrophil count 1.7 ± 1.30 x 10⁹/L, lymphocyte count 5.0 ± 2.2 x 10⁹/L, mean C-reactive protein 4.0 ± 4.5 mg/L, AST 50 ± 14.8 U/L, ALT 24 ± 10.7 U/L, LDH 385 ± 96.6 U/L. 57.5% of the patients had neutropenia (10% severe, 35% moderate and 12.5% mild) and neutropenia resolved in one months. Mean lymphocyte/neutrophil rate was calculated as 2.94 (relative lymphocytosis). None of the patients experienced infections secondary to neutropenia and febrile convulsion.

Özet

Giriş: Bu çalışmanın amacı 2012-2016 yılları arasında yüksek ateş, döküntü nedeniyle polikliniğimize başvuran klinik olarak roseola infantum tanısı konan 46 hastanın demografik ve laboratuvar bulgularından edinilen deneyimi paylaşmaktır.

Gereç ve Yöntemler: Klinik olarak roseola infantum tanısı konan 41 hastanın laboratuvar ve demografik bulguları değerlendirildi. Hastalığın tanısı ateş ve döküntüye neden olabilecek diğer hastalıkların ayırıcı tanısı yapıldıktan sonra, "üç günden beri devam eden yüksek ateş, toksik olmayan 10 aylık bir bebeğin gövdesinde makülopapüler döküntü" olması roseola infantum olarak değerlendirildi. Nötrofil sayısı 0-500 ise ağır, 500-1000 ise orta, 1000-1500 ise hafif nötropeni olarak değerlendirildi.

Bulgular: Hastaların 25 (%54.3)'i kız, 21 (%45.7)'i erkek, yaş ortalaması 11.5 ± 7.02 (3-36 ay) ve başlangıç pik yaşı 9-11 ay idi. Hastaların %76'sı (35/46) bir yaşın altında idi. Hastalık tüm yıl boyunca görülmekle birlikte en az Eylül ve Ekim ayında, en çok Aralık ayında gözlendi. Hastaların sırasıyla ortalama Hb 11.8 ± 0.97 g/L, HCT %35.0 ± 3.2, MCV 73.7 ± 5.10 fL, trombosit sayısı 299 ± 128.8 x 10⁹/L, lökosit sayısı 7.5 ± 2.8 x 10⁹/L, nötrofil sayısı 1.7 ± 1.30 x 10⁹/L, lenfosit sayısı 5.0 ± 2.2 x 10⁹/L, ortalama C-reaktif protein (CRP) değeri 4.0 ± 4.5 mg/L, AST 50 ± 14.8 U/L, ALT 24 ± 10.7 U/L, LDH 385 ± 96.6 U/L olarak bulundu. Hastaların %57.5'inde nötropeni (%10 ağır, %35 orta ve %12.5 hafif) vardı. Ortalama lenfosit/nötrofil oranı 2.94 (rölatif lenfositoz) olarak hesaplandı. Hastaların hiçbirinde nötropeniye sekonder enfeksiyon ve febril konvülzyon gözlenmedi.

Sonuç: Nötropeni, relatif lenfositoz, hafif AST yüksekliği ve CRP negatifliği saptanan üç yaşın altındaki çocuklarda (özellikle bir yaşın altındaki

Correspondence Address /Yazışma Adresi

Zafer Bıçakçı
Kafkas Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı,
Çocuk Hematolojisi Ünitesi, Kars-Türkiye

E-mail: zaferbicakcib@yahoo.com.tr

Conclusion: Under three years of age children (especially young infants) with fever without source accompanying neutropenia, relative lymphocytosis, mild AST elevation and negative CRP roseola infantum should be considered as an etiological factor.

Keywords: Fever, C-reactive protein, relative lymphocytosis, roseola infantum

bebeklerde) kaynağı saptanamayan ateş nedeni olarak roseola infantum da akla gelmelidir.

Anahtar Kelimeler: Ateş, C-reaktif protein, geçici nötropeni, relatif lenfositoz, roseola infantum

Introduction

Roseola infantum is an acute viral infection, particularly observed in infants and play-age children and characterized by clinical manifestations of fever of unknown origin and widespread maculopapular rashes which develop following reduction in the fever. Human herpesvirus (HHV) -6 and HHV-7 (approximately two-third, HHV-6 and one-fourth, HHV-7) are responsible for most cases of Roseola infantum. Two different variants of HHV-6, namely HHV-6A and B differ in terms of their genetic, biological, and immunological properties. Almost all HHV-6B (more than 99%) produce a clinical picture of roseola infantum, while HHV-6A constitutes the majority of childhood infections in some African communities (1-3).

Patients with roseola infantum present with a clinical picture of fever of unknown origin, and it may be difficult to make a differential diagnosis at baseline. Diagnosis is usually made after the patient's typical course has been observed (4,5). Acute HHV-6 infection is responsible for 20% of children who come to the emergency department due to febrile illness among 6-8 months old children. About 13% of these children are hospitalized (6). These findings point to an important economics of HHV-6 infection and emphasize the importance of making the right differential diagnosis to avoid unnecessary antibiotic use. As a result, it may be worthwhile to develop a quick, simple test for this self-limiting infectious disease, without applying unnecessary treatment and/or expensive laboratory tests (7).

In acute phase response, the synthesis of a number of proteins is under the control of cytokines originating from the site of the pathology and the synthesis of these proteins is particularly fast in the liver (8). This response is proportional to the severity of the inflammatory stimulus and is mediated by proinflammatory cytokines such as interleukin (IL)-6, IL-1, tumor necrosis factor-alpha (TNF-α) and interferon-gamma (INF-γ). Fever is also one of the acute phase responses to infection or inflammation through proinflammatory cytokines. CRP, another product of acute phase response, is produced primarily by the liver in response to cytokines, primarily IL-6 (9). Although HHV-6 is a potent stimulator of TNF-α and IL-1β in peripheral blood mononuclear cell cultures, HHV-6 has no effect on IL-6 synthesis. This may be the reason why the CRP level does not increase as an acute phase reactant despite the presence of fever during HHV-6 infection (10). Transient neutropenia has also been reported in primary HHV-6 infection (10,11). In addition to the inability to synthesize IL-6, which stimulates neutrophil production during primary HHV-6 infection, the suppression of bone marrow progenitor cells may also be responsible for transient neutropenia (12-14).

HHV-6 antigens, nucleic acids and antibodies are used in the detection of viral infection. At the time of initial evaluation, there is no definite diagnostic, easily distinguishable, or sufficiently specific clinical or laboratory finding for HHV-6 primary infection (15). Since tests used for the definitive diagnosis of the disease take a certain amount of time to produce results, it can be considered as a non-practical approach to the immediate emergency diagnosis of the patient. As a result, some hematological laboratory values considered to be more practical than predicting the disease (roseola infantum) in emergency conditions, may act as a clue.

In the present study, we aimed to evaluate the demographic and laboratory findings of patients who had a pre-clinical diagnosis of roseola infantum in our polyclinic due to high fever/rash, and to identify findings which would be useful for a rapid diagnosis of the condition.

Materials and Methods

Data of this descriptive study were obtained from 46 patients who visited our outpatient clinic between the period of 2012-2016 and who were pre-diagnosed with roseola infantum.

Information Obtained From Files

Pre-diagnosis of the disease, age of the patient, gender, season during which it was reported, hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), total platelet count, total leukocyte, neutrophil count, lymphocyte count, C-reactive protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) values were used. The laboratory data of five patients were not found in the files. As a result, demographic and seasonal characteristics were evaluated on 46 patients whereas laboratory characteristics were evaluated on 41 patients.

Picture 1. Typical maculopapular eruptions in the torso of a child with roseola infantum.

Definitions of Variables

The diagnosis of roseola infantum was made from the "high fever that lasted for three days, and maculopapular rash on the chest of a 10-month-old non-toxic baby" after making a differential diagnosis from other diseases that may cause fever and rash (Picture 1) (5).

A neutrophil count of 0-500 was evaluated as severe, 500-1000 as moderate and 1000-1500 as mild neutropenia (10).

Low risk criteria was defined as: laboratory findings which did not show any indication for a risk of severe bacterial infection, a leukocytes count of between 5-15.000/mm³ from the complete blood count, bands count of less than 1.500/mm³, and C-reactive protein of less than 20 mg/L (16,17).

High-risk criteria was defined as: laboratory findings which indicated a risk of severe bacterial infections, a leukocyte count of less than 5.000/mm³ or above 15.000/mm³ or bands count of more than 1.500/mm³, from the complete blood count, and C-reactive protein of more than 20 mg/L (16,18).

Statistical Analysis

SPSS package program (IBM, Chicago, USA) was used for the statistical calculations of this research. Frequencies, persentages, measures of central tendency (mean and median values) and measures of variability (standard deviation, minimum and maximum values) were used in this study.

Results

Twenty-five (54.3%) of the patients were female while 21 (45.7%) were male. The mean age was found to be 11.5 ± 7.02 (3-36 months), while the median age was 10.0 months. The baseline peak age of the disease was 9-11 months. Seventy-six percent (35/46) of the patients were under one year of age (Figure 1). The disease was observed throughout the year, least in September and October, but mostly observed in December (Figure 2). Forty-one of the patients had laboratory data (Table 1). Neutropenia was detected in 57.5% (23 patients) of the 40 patients with neutrophil values. Neutropenia was reported to be severe in 10.0% (n= 4) of the patients, moderate in 35% (n= 14) and mild in 12.5% (n= 5) of the patients (Table 2). Neutropenia improved within a period of about one month. The mean lymphocyte/neutrophil ratio was calculated as 2.94. None of the patients reported secondary infection and febrile seizures to neutropenia. All of our patients had low risk criteria for infection.
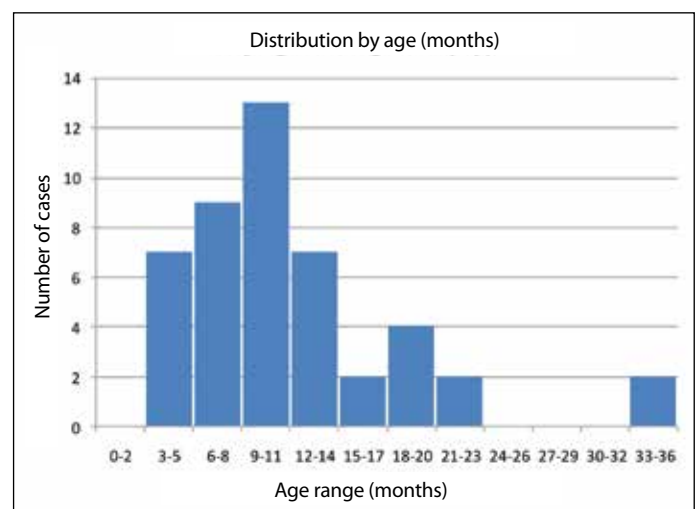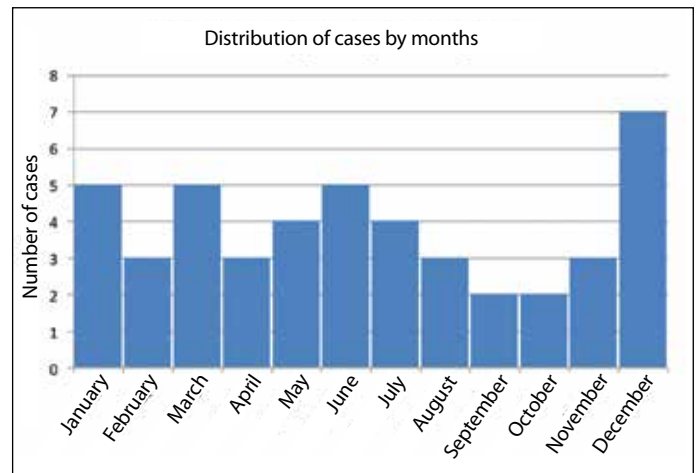

Figure 1. According to the age chart, there was a rapid increase in the number of cases from 3 months till between 9-11 months, followed by a relatively slower decline from 21-23 months.

Table 1. Mean hemogram and C-reactive protein values of the patients

	Hb g/L	HCT %	MCV fL	Thrombocyte x10⁹/L	Leukocyte x10⁹/L	Neutrophil* x10⁹/L	Lymphocyte x10⁹/L	Monocyte x10⁹/L	Basophil	Eosinophil	CRP mg/L	AST U/L	ALT U/L	LDH U/L
Mean	11.8	35.0	73.7	299.0	7.5	1.7	5.0	0.52	0.08	0.17	0.40	50.00	24.00	385.00
Median	12.0	34.6	73.7	266.0	7.7	1.1	5.2	0.50	0.05	0.10	0.25	45.00	21.00	372.00
Standard deviation (±)	0.97	3.2	5.1	128.8	2.8	1.3	2.2	0.30	0.09	0.14	0.45	14.80	10.70	96.60
Minimum	9.2	26.7	61.6	127.0	2.8	0.2	1.4	0.13	0.00	0.00	0.01	23.00	5.00	221.00
Maksimum	14.1	41.2	82.4	833.0	15.2	15.1	12.2	1.28	0.44	0.55	2.00	87.00	61.00	725.00

* 40 of the patients had neutrophil values. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, Hb: Hemoglobin, HCT: Hematocrit, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume.

Figure 2. The disease was observed throughout the year, least in April and September, but mostly observed in December.

Table 2. Mean neutrophil counts and percentages of patients

Neutrophil count	Number of patients	Percentage %
0-500	4	10.0
500-1000	14	35.0
1000-1500	5	12.5
> 1500	17	42.5
Total	40	100

Discussion

The most common finding in children with HHV-6 primary infection is fever (19). The disease starts suddenly with a fever. The fever may rise up to ≥ 40°C. Symptoms of mild upper respiratory tract infection and cervical lymphadenopathy may coexist. The fever persists for 3-5 days without a typical finding for the disease. Febrile convulsions may be observed during this period. The overall appearance of the patient is relatively good, although the fever may be high. Fever falls on the 3rd - 5th days in the form of crises, and macular or maculopapular eruptions start appearing from the body (torso), spreading to the arms, neck, face and legs, as the fever returns to normal. The eruptions are short-lived, rarely lasting for more than 24 hours (1).

Patients with roseola infantum present with a clinical picture of fever of unknown origin, and it may be difficult to make a differential diagnosis at baseline. Diagnosis is usually made after the patient's typical course has been observed (4,5). Approximately 58-98% of children with HHV-6 infection have fever, and about 17-98% has been reported to have eruptions of

roseola infantum. The reasons for these varying percentages can be explained by the existence of different research layouts, differences in inclusion research criteria, geographical differences and the presentation of different tropism of various viral types (19,20). Although roseola infantum is often a benign disease which is self-restricting, the diagnosis of roseola infantum may be made by excluding the other more serious disorders that cause fever and skin eruptions. In addition, the maculopapular skin eruption in the non-toxic 10-months-old baby's torso, with symptoms of high-fever suggests the diagnosis of roseola infantum (5). Clinical diagnosis in all of our patients was made after observation of post-fever classical/typical roseola infantum eruptions, the presence of low risk criteria in the laboratory analysis, and after excluding the other diseases that cause fever and eruptions. We suggest that clinical, laboratory, and demographic data may be a clue for predicting the presence of roseola infantum when determining the cause of fever of unknown origin in an outpatient setting.

The disease is sporadic in nature. Unlike with other diseases with eruptions, there is no history of contact with persons suffering from this disease when evaluating children with roseola infantum. The disease is not expected to cause an epidemic. The disease can be seen worldwide, throughout the year (2,5,21,22). The absence of a history of contact in these patients and the fact that it can be observed throughout the year and in a sporadic form, is consistent with literature studies.

Although newborn cases with HHV-6 infection have been reported even though antibodies are passed from the mother, most babies are protected from the disease in the first months of life due to the antibodies passed on from the mother (22). The prevalence of anti-HHV-6-IgG antibody in the mothers of newborns was found to be 71.9%. The rate of passive antibody decline between the second and sixth months is reported as 23.2% (23). Serological studies have shown that most children have a HHV-6 infection before the age of three, particularly between 6-15 months (1). Antibody positivity rates among different age groups of HHV-6 were found to be 69.2% between 7-12 months, 71.6% between 13-24 months and 79.8% between 3-5 years (23). The HHV-7 infection is observed at a slightly later age than the HHV-6 infection. About 50% of children until the age of three, 75% of children aged 3-6 years, 90% of adults are seropositive for HHV-7 (5,24). The absence of any cases up to the first two months and the fact that 75% of the cases are from three months up to 12 months, is consistent with literature studies with regards to it coinciding with the period of passive antibodies decline.

HHV-6 may suppress all bone marrow cell lines. HHV-6 infection may result in a decrease of MHC type I response on the immune system, increased NK cell activity, suppression of peripheral blood mononuclear cell proliferation, and induction of proinflammatory cytokine response (24,25).

CRP is produced within 4-6 hours after the onset of inflammation or tissue damage. CRP doubles every eight hours before reaching the highest value at around 36 hours (18). The level of CRP is often below 2 mg/L in healthy individuals, but may rise up to 10 mg/L. It may vary slightly with age, gender, and race. Its half-life is about 19 hours (8).

Acute HHV-6 infection stimulates cellular immunoregulatory mediators (IL-1, INF-α, INF-γ, TNF-α) and natural killer (NK) cell cytotoxicity (1,26-29). Monocyte and monocyte-derived dendritic cells are targets of HHV-6 in the pathogenesis and immunosuppressive effect during acute infection (30,31). Increased proinflammatory cytokine secretion such as interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α) and interferon-α (INF-α) is observed in peripheral blood mononuclear cells during HHV-6 infection, and NK cell activity is also observed to increase together with IL-15 synthesis. Although HHV-6 is a potent stimulator of TNF-α and IL-1β in peripheral blood mononuclear cell cultures, HHV-6 has no effect on IL-6 synthesis (26,32). The CRP level should be below 20 mg/L to rule out severe infections (16). The mean CRP value was reported as 4.0 mg/L in our patients. The fact that CRP, the acute phase reactant does not increase despite the presence of fever in all patients, may be the reason why the major CRP stimulant IL-6 cannot be synthesized. As a result, we believe that the increase in CRP despite the presence of fever may be an indirect indicator of primary HHV-6 infection.

HHV-6 may suppress all bone marrow cell lines (13,14). As a result, neutropenia may first develop, followed by thrombocytopenia (10,11,33). During the first few days of fever in patients with roseola infantum, the mean leucocyte count is around 8-9.0 x 10⁹/L, with a neutrophil dominance. The mean leukocyte count at the time of onset of eruptions decreases by 4-6.0 x 10⁹/L, and relative lymphocytosis (70-90%) is observed (34). We are of the opinion that the fact that the mean leukocyte count was 7.5 ± 2.8 x 10⁹/L, that some of the patients had fever while the leukocyte count was measured in some during the eruption period suggests that it was an intermediate value.

The mean age of our patients was 11.5 ± 7.02. As a result, the mean leukocyte count of a healthy one-year-old child is 11.4 x 10⁹/L, the neutrophil count is 3.5 x 10⁹/L, the lymphocyte count is 7.0 x 10⁹/L and the monocyte count is 0.6 x 10⁹/L (35). The normal value defined for a one year old was found to be low, since the mean leucocyte count was 7.5 ± 2.8 x 10⁹/L, neutrophil count was 1.7 ± 1.30 x 10⁹/L, lymphocyte count was 5.0 ± 2.2 x 10⁹/L and monocyte count was 0.52 ± 0.30 x 10⁹/L. Hence, partial bone marrow progenitor cell suppression and a decrease in transient leukocyte counts can be suggested. The normal lymphocyte/neutrophil ratio for a child of one year is approximately (7.0/3.5) 2 (35). Relative lymphocytosis (75%) can be suggested, as the lymphocyte/neutrophil ratio

(5.0/1.7) of our patients is about 3. Our study is consistent with the literature studies as a result. IL-6 usually stimulates neutrophil production from bone marrow progenitor cells together with colony stimulating factors (12). We are of the opinion that transient reductions in leukocyte counts and transient neutropenia (57.5%) can occur due to the inhibition of IL-6 synthesis during primary HHV-6 infection and the suppression of bone marrow progenitor cell lines.

HHV-6 has a distinguishable cytopathic effect consisting of the appearance of large refractile mononucleated or multinucleated cells with intracytoplasmic and/or intra-nuclear inclusions. In the culture medium, infected cells demonstrate a some what long half-life, dominated by lytic infection. HHV-6 infection also stimulates apoptosis of T cells and leads to the death of the cell through retinoic acid-induced cell death, signals and interferon exchange, as well as mitochondrial membrane potential loss (5). ALT in the cell is found only in the cytosol, whereas AST is found both in the mitochondria and cytosol. Therefore, AST elevation is more prominent in diseases affecting the mitochondria (36). In patients with primary HHV-6 infection and severe neutropenia, AST is reported to be 50 U/L and ALT 18 U/L, whereas in patients without neutropenia AST is 44 U/L and ALT 19 U/L (10). A mean AST of 50 U/L and ALT of 24 U/L were detected in our patients. Since AST demonstrates cell lysis/necrosis, AST elevation may be a clue for patients with primary HHV-6 infection affecting the mitochondria.

After the fever falls and the eruptions appear, the disease should be differentiated from other maculopapular eruption diseases such as measles, rubella, scarlet fever, enteroviral infections, and drug reactions (5). Roseola infantum may be very difficult to distinguish from other common viral infections during childhood. Primary infection with HHV-6 or HHV-7 is often indistinguishable from febrile diseases. This difficulty also applies to the early stages of roseola before skin eruptions develop. In the presence of skin eruptions, roseola can be confused with other exanthematous diseases of childhood, particularly measles and rubella. Unlike roseola, the typical symptoms of measles are gastrointestinal complaints, arthralgia, sore throat, low fever and mild disease. On physical examination, the sub-occipital and posterior auricular lymph nodes are detected before the eruptions of rubella occur and continue during the eruption phase. In addition, rubella eruptions start on the face and spread to the torso in a similar manner to measles.

Unlike with roseola, symptoms associated with measles virus infection include high fever, cough, coryza, and conjunctivitis, with concomitant development of skin eruptions.

Roseola may also be confused with the rarely reported scarlet fever seen in children under the age of two. Scarlet fever causes a characteristic sand paper-like skin eruption which occurs concomitantly with fever.

Roseola can be confused with diseases that cause enterovirus infection, particularly in summer and autumn. Enterovirus infections are mostly in the form of hand-foot-mouth disease and the skin eruption is in the form of papulo-vesicles. In addition, fever and rubelliform rash are observed concomitantly.

It may also be difficult to differentiate drug allergies from roseola. Antibiotics are often prescribed for people with roseola fever before skin eruptions are observed. A child with skin eruptions after a fever has subsided is mistakenly described as having a drug allergy. Our patients had no history of drug use.

No similar study has been reported in Turkey about roseola infantum of childhood. Despite the absence of serological and virological (PCR, PCR) evidence of HHV-6 infection in our study, this study was consistent with the studies reported in the literature in terms of age group of the patients, peak age observed, gender and observation throughout the year. This may also be an indirect proof that HHV-6 infection has occurred.

In conclusion, roseola infant should be considered as a cause of fever of unknown origin in children less than three years of age (particularly in infants below the age of 6) who undertook simple laboratory tests and neutropenia, relative lymphocytosis, mild AST elevation and CRP negativity that were detected under emergency conditions.

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