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REVIEW ARTICLE

Roseola Infantum: An Updated Review

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Abstract: ***Background*:** Roseola infantum is a common viral disease that occurs during childhood worldwide.

***Objective*:** The purpose of this article is to familiarize pediatricians with the clinical manifestations, evaluation, diagnosis, and management of roseola infantum.

Methods: A search was conducted in April, 2022, in PubMed Clinical Queries using the key terms "roseola infantum" OR "exanthem subitum" OR "sixth disease". The search strategy included all clinical trials, observational studies, and reviews published within the past 10 years. Only papers published in the English literature were included in this review. The information retrieved from the above search was used in the compilation of the present article.

Results: Roseola infantum is a viral illness characterized by high fever that lasts 3 to 4 days, followed by the sudden appearance of rash at defervescence. The disease occurs most frequently in children between 6 months and 2 years of age. Human herpesvirus-6 (HHV-6) is the major cause of roseola infantum, followed by HHV-7. Transmission of the infection most likely results from the asymptomatic shedding of the virus in the saliva of the caregivers or other close contacts. Characteristically, the rash is discrete, rose-pink in color, circular or elliptical, macular or maculopapular, measuring 2 to 3 mm in diameter. The eruption is first seen on the trunk. It then spreads to the neck and proximal extremities. Typically, the rash blanches on pressure and subsides in 2 to 4 days without sequelae. Most children look well otherwise and appear to be happy, active, alert, and playful. The diagnosis is mainly clinical. Febrile seizures occur in 10 to 15 % of children with roseola infantum during the febrile period. In general, serious complications are rare and occur more often in individuals who are immunocompromised. There is no specific treatment. An antipyretic may be used to reduce fever and discomfort.

Conclusion: Roseola infantum is generally a benign and self-limited disease. Failure to recognize this condition may result in undue parental fear, unnecessary investigations, delay in treatment for conditions that mimic roseola infantum and complications from roseola infantum, unnecessary treatment of roseola infantum *per se*, and misuse of healthcare expenditure.

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1. INTRODUCTION

Roseola infantum (also known as exanthem subitum, sixth disease, baby measles, three-day fever) is a common childhood disease characterized by a high fever that lasts 3 to 4 days, followed by the sudden appearance of a morbilliform rash at defervescence [1]. The condition was the sixth common childhood exanthem to be named after measles, scarlet fever, rubella, Filatov-Dukes disease (atypical scarlet fever), and erythema infectiosum. Roseola infantum is a significant cause of febrile seizures. The condition was first described in the medical literature as a unique clinical entity by Robert Willan in 1809 [2, 3], and the term "roseola infantum" was coined by John Zahorsky in 1910 [4]. The etiologic agent was not identified until 1988 by Yamanishi *et al*. [5]. Roseola infantum is often misdiagnosed as an adverse drug reaction or as other childhood exanthems, such as measles, rubella, and scarlet fever.

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A search was conducted in April, 2022, in PubMed Clinical Queries using the key terms "roseola infantum" OR "exanthem subitum" OR "sixth disease". The search strategy included all clinical trials (including open trials, non-randomized controlled trials, and randomized controlled trials), observational studies, and reviews (including narrative reviews and meta-analyses) published within the past 10 years. Only papers published in the English literature were included in this review. The information retrieved from the above search was used in the compilation of the present article.

2. PREVALENCE

Roseola infantum occurs worldwide with no racial or geographical predilection [6]. The condition occurs most frequently in children between 7 months and 13 months of age [1]. Presumably, maternally acquired antibodies protect most infants from the disease during the first few months of life [7, 8]. Roseola infantum has rarely been reported in the neonatal period [9]. In the United States, roseola infantum accounts for 10 to 45% of febrile illnesses in infants and approximately 12% of visits to the emergency department for febrile infants [10, 11]. By 12 and 18 months of age, approximately 65 and 95% of children, respectively, have become infected [7]. Almost all children have acquired the infection by 2 years of age [12, 13]. Roseola infantum is rare after 4 years of age [14]. The sex ratio is approximately equal. Although roseola infantum occurs throughout the year, the peak incidence is in the spring and autumn [1, 6]. Occasionally, roseola infantum occurs in outbreaks in closed populations [15-17].

3. ETIOLOGY AND PATHOGENESIS

Roseola infantum is most frequently caused by human herpesvirus-6 (HHV-6), less frequently by HHV-7, and rarely by enterovirus and parvovirus [18-36]. Both HHV-6 and HHV-7 are large, spherical, enveloped, linear, double-stranded deoxyribonucleic acid (DNA) viruses with an icosahedral capsid and a protein-rich tegument layer that is surrounded by a membrane [37, 38]. These viruses have an envelope of 160 to 200 nanometers in diameter, and their genomes encode approximately 100 proteins [12, 31, 39, 40]. Both HHV-6 and HHV-7 are ubiquitous in human beings [38, 39, 41]. They are members of the Roseolovirus genus of the Herpesviridae family and Betaherpesvirinae subfamily and are genetically related to human cytomegalovirus [12, 39, 40]. HHV-6 has two variants, namely, HHV-6A and HHV-6B, based on their genome sequence (>90% sequence homology), antigenicity, immunological features, and biological characteristics [6, 17, 40]. HHV-6A seems to be more cytolytic and potentially more virulent than HHV-6B. HHV-6B is the major cause of roseola infantum and accounts for more than 95% of primary HHV-6 infections in children in the United States and the United Kingdom [6, 13, 42]. On the other hand, HHV-6A is more common in African children and is an uncommon cause of roseola infantum [6]. These viruses are trophic for CD4+ T lymphocytes, in which they replicate and may disseminate widely [13, 24, 43]. It has been shown that the magnitude of viral replication and viremia correlates with the severity of clinical features in infants with roseola infantum [44]. HHV-6A and HHB-6B bind to the CD46 and CD134 of cellular receptors in the cell membrane, respectively [11, 13, 39]. *Via* receptor-mediated endocytosis, the nucleocapsid is transported through the cytoplasm, and the viral DNA genome migrates to the cell nucleus, where viral replication takes place [11, 13, 39, 45]. HHV-6 persists in peripheral blood mononuclear cells, salivary glands, and the central nervous system [6, 17, 40]. On the other hand, HHV-7 binds to the CD4 receptor to infect and establish latency in T lymphocytes; active replication of HHV-7 occurs in salivary glands [6, 17, 40]. HHV-6 utilizes a number of strategies to downgrade the host's immune system, including augmentation of natural killer T-cell activity, suppression of peripheral blood mononuclear cell proliferation, and induction of numerous cytokines, such as interferon-α (most common), interferon–γ, interleukin -1β, interleukin-8, interleukin-10, and interleukin-15 [40, 46, 47]. HHV-7 also enhances interleukin-15 and natural killer activity [6]. Both HHV-6 and HHV-7 have the capability to establish lifelong latency in immune cells and tissues of the host following a primary infection [17, 48]. DNAs of HHV-6 and HHV-7 can be detected from several body sites intermittently or persistently in patients with roseola infantum [49].

Most cases of roseola infantum occur sporadically, without a history of known exposure [50, 51]. Transmission of the infection likely results from the asymptomatic shedding of the virus in the respiratory droplets and saliva of the caregivers, siblings, or other close contacts, especially in the convalescent phase of roseola infantum [6, 52]. Less commonly, the infection is acquired by contact with respiratory droplets and saliva of an affected individual during the febrile and viremic phase of the illness. The main route of transmission is through inoculation of the oropharynx, leading to the replication of the virus in salivary glands [53]. From the salivary glands, the virus gains access to T-lymphocytes [53]. Patients are viremic from 2 days prior to the fever until defervescence [24]. Presumably, the rash results from antigen-antibody complexes as its development coincides with the development of antibodies to HHV-6 and HHV-7 [1, 25, 54]. HHV-7 infection tends to occur somewhat later in life than HHV-6 infection and is usually acquired at a median age of 26 months [12, 17, 24]. The majority of primary infections with HHV-7 are mild or asymptomatic, although some may present as roseola infantum [12]. Both HHV-6A, HHV-6B, and HHV-7 establish lifelong latency after initial acquisition and may reactivate and account for recurrent cases of roseola infantum [12, 24].

4. CLINICAL MANIFESTATIONS

The incubation period for HHV-6 is 9 to 10 days, whereas that for HHV-7 is not known [7, 12, 54, 55]. During the prodromal period, the child is usually asymptomatic but may experience minimal rhinorrhea, cough, vomiting, diarrhea, sore throat, and conjunctivitis [6, 55]. Roseola infantum is characterized by a high fever that lasts 3 to 4 days, followed by the sudden appearance of rash at defervescence (hence the term "exanthem subitum" meaning "sudden rash"; subitum

is the Latin word for sudden) [53, 56]. The fever has an abrupt onset [53, 56]. The temperature is characteristically in the range of 39 to 40.5°C, and the fever can be intermittent or constant [17, 53, 57]. Most children look well otherwise and appear to be happy, active, alert, and playful [24, 50-52]. However, some children may exhibit periods of restlessness and irritability during times of high fever. With a sudden resolution of the fever, the typical exanthem appears [57]. Characteristically, the rash is discrete, rose-pink in color, circular or elliptical, macular or maculopapular, measuring 2 to 3 mm in diameter (Figs. **1** and **2**) [17, 53]. Rarely, the rash is vesicular [58]. The eruption begins on the trunk and spreads to the neck, face, and extremities [24]. Typically, the rash blanches under pressure and subsides in 2 to 4 days [53]. In some cases, a halo of pale skin can be found around some of the lesions [11]. Characteristically, lesions remain discrete but occasionally may become confluent [6]. Desquamation and pruritus are characteristically absent [17, 53]. Suboccipital (most frequent), postauricular and cervical lymphadenopathies are common [59-62]. The enlarged lymph nodes are usually not prominent, although they may be tender [51]. Other clinical findings include palpebral and periorbital edema (Berliner sign) (Fig. **3**), conjunctival erythema, injected tympanic membrane (Fig.**4**), erythema of the pharynx, soft palate, and uvula (Fig. **5**), erythematous maculopapular spots on the soft palate and uvula (Nagayama spots), and uvulo-palatoglossal junctional ulcer [63-67]. Some authors suggest that a uvulo-palatoglossal junctional ulcer is a reliable early sign of roseola infantum, which can be seen prior to the eruption of the rash [64-67]. A bulging fontanelle in the absence of meningitis or encephalitis may be present [68, 69]. Presumably, the bulging fontanelle is due to intracranial hypertension caused by HHV-induced cytokine elevation with resultant increased cerebrospinal fluid production [68]. In a study on 176 infants (94 boys and 82 girls) with roseola infantum, palpebral and periorbital edema was observed in 30% of cases, erythematous papules in the pharynx in 65% of cases, and bulging of the anterior fontanelle in 15% of cases [54].

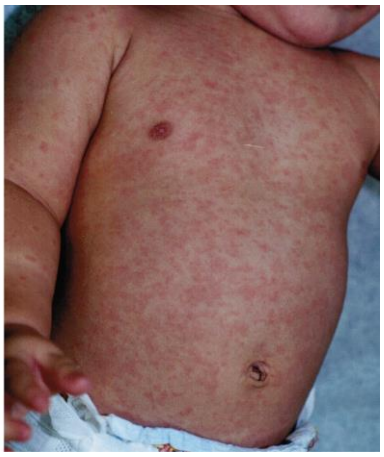

Fig. (1). Discrete rose-pink macules and maculopapules rash located primarily on the trunk and neck of an infant with roseola infantum. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

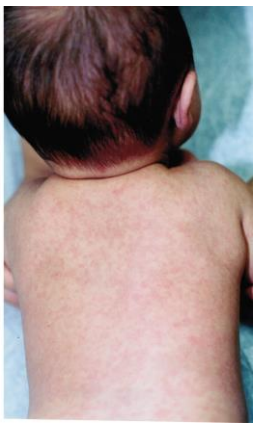

Fig. (2). Discrete rose-pink macules and maculopapules characteristics of roseola infantum on the back of an infant with fever for three days; the appearance of the rash followed defervescence. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

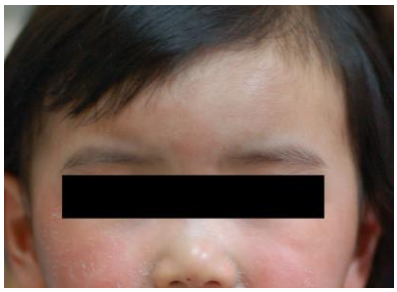

Fig. (3). Mild palpebral and periorbital edema in a child with roseola infantum. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

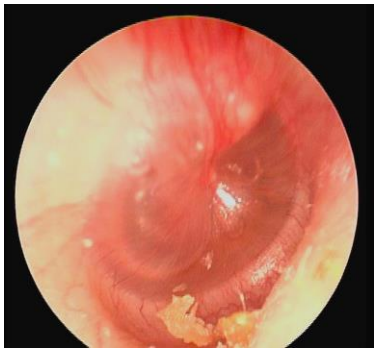

Fig. (4). Injected tympanic membrane in a child with roseola infantum. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

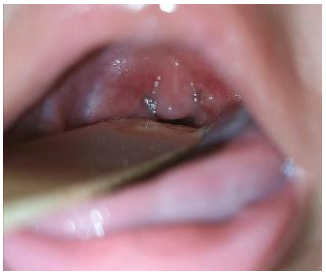

Fig. (5). Erythema of the soft palate, uvula and pharynx in a child with roseola infantum. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5. DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is mainly clinical, based on the characteristic features (high fever for 3 to 4 days, sudden appearance of a morbilliform rash at defervescence). Drug allergy is an important consideration in a febrile child who is receiving antimicrobial therapy and develops a rash. With a drug allergy, the rash usually lasts longer, and pruritus and fever may accompany the rash. As children with roseola infantum may have inflamed tympanic membranes, they may be misdiagnosed with acute otitis media and mistreated with antibiotics. In infants, the diagnosis of acute otitis media can be quite difficult because symptoms are often nonspecific and include fever, poor feeding, apathy, irritability, inconsolable crying, restless sleep, tugging or poking at the affected ear or placing their palm over the affected ear [70, 71]. In older children, the presenting symptoms include earache, ear stuffiness, hearing loss, "popping" or "snapping" sounds in the ear, and otorrhea, which will make the diagnosis a lot easier [70].

In the pre-eruptive stage, urinary tract infection may be a diagnostic consideration in a child with a fever. The diagnosis can be difficult as children with roseola infantum may have sterile pyuria [72]. In addition, in the first two years of life, symptoms of urinary tract infection are often nonspecific and include unexplained fever (most common or maybe the only presenting symptom), poor feeding, irritability, anorexia, and failure to thrive [73-77]. Specific symptoms, when present, include malodorous urine, an increased number of wet diapers, and discomfort with urination.

Roseola infantum may be confused with many other conditions with fever and rash, such as nonspecific viral exanthems, measles, rubella, hand, foot, and mouth disease, erythema infectiosum, infectious mononucleosis, scarlet fever, and Kawasaki disease [78]. In general, children with roseola infantum have a significantly higher mean temperature than those with other febrile exanthems, with the great majority of children having temperatures greater than 39°C [79]. In addition, the distinctive features of other febrile exanthems generally allow for a straightforward differentiation from roseola infantum to be made.

Nonspecific viral exanthems can be differentiated from roseola infantum based on prodromal symptoms, characteristics of the rash, time of appearance of the rash in relation to the fever, associated symptoms, such as conjunctival injection, rhinorrhea, cough, and cervical lymphadenopathy, epidemiology, and the season in which they occur.

Children with measles, also known as rubeola, typically present with a prodromal illness characterized by fever and the classic triad of three "C"s: cough, coryza, and conjunctivitis. Bluish-white papules simulating "grains of sand or ice" on an erythematous base on the buccal mucosa (Koplik spots), when present, are pathognomonic [80-83]. A characteristic, erythematous to purple-red, morbilliform exanthem appears 3 to 4 days after the onset of fever which intensifies with the appearance of the exanthem [84-86]. The exanthem typically begins on the face and spreads to the trunk and extremities [81, 86]. The exanthem fades in 5 to 10 days in the same directional pattern as it appears [82, 83].

Children with rubella typically present with an extensive rash that occurs simultaneously with fever (usually low-grade) and prominent occipital, postauricular, and posterior cervical lymphadenopathy, which often becomes more pronounced with the onset of the rash [87, 88]. The exanthem consists of a pinpoint erythematous maculopapular rash, which classically begins on the face, spreads caudally to the trunk and extremities, and becomes generalized within 24 hours [88, 89]. The rash usually lasts for three days and fades in the same directional pattern it appeared [87]. In approximately 20% of cases, petechiae can be observed on the soft palate (Forchheimer spots) [90].

The characteristic findings in patients with hand, foot, and mouth disease are a painful oral enanthem and an asymptomatic exanthem. Oral lesions occur chiefly on the anterior buccal mucosa and tongue and present initially as erythematous macules, which rapidly progress to vesicles surrounded by a thin halo of erythema [91-94]. The vesicles eventually rupture, leaving superficial ulcers with a grey-yellow base and erythematous borders. The exanthem typically involves palms and soles and consists of macules, maculopapules, papules, papulovesciles, or vesicles on a surrounding zone of erythema [95, 96]. Some affected children may have a low-grade fever, which usually resolves in 24 hours [96].

Erythema infectiosum, also known as the fifth disease, is characterized by an erythematous rash on the cheeks, with a "slapped cheek" appearance [97, 98]. A circumoral pallor is usually present. The rash then spreads concurrently or quickly to the trunk, extremities, and buttocks as diffuse macular erythema [97, 98]. The rash tends to be more intense on extensor surfaces. Central clearing of the rash results in a characteristic lacy or reticulated appearance. The rash usually resolves spontaneously within 3 weeks. Prodromal symptoms are usually mild or absent. Some children may have nonspecific symptoms, such as low-grade fever, coryza, headache, malaise, and myalgia [97, 98].

Children with scarlet fever commonly present with sudden onset of fever, sore throat, a beefy red pharynx, enlarged and erythematous tonsils, enlarged tender anterior cervical lymph nodes, and a rash [99-101]. The rash typically blanches on pressure, has the texture of gooseflesh or coarse sandpaper, and is better felt than seen [99-101]. Confluent petechiae may be noted in flexor skin creases, especially in the antecubital fossae (Pastia lines) [91, 99].

Infectious mononucleosis, also known as the "kissing disease", is characterized by the classic triad of fever, pharyngitis, and cervical lymphadenopathy, where lymphocytosis and atypical lymphocytes are also present. A nonpruritic rash is seen in approximately 10 to 45% of cases, typically during the first few days of the illness and lasting 1 to 6 days [102, 103]. The rash is widely scattered, erythematous, and morbilliform or maculopapular [103]. Between 30 and 90% of patients treated with amoxicillin or ampicillin experience a pruritic maculopapular rash [104]. Fatigue may be profound but tends to resolve within three months [103]. Splenomegaly and hepatomegaly occur in approximately 50% and 10% of cases, respectively [102].

Kawasaki disease is characterized by fever (>39ºC and swinging) for at least five days, conjunctival injection (typically bilateral, nonexudative, and nonpurulent; primarily bulbar with sparing of the limbus), polymorphous rash (diffuse, erythematous, maculopapular, and nonpruritic), oral mucosal changes (erythema, dryness, fissuring, cracking, swelling, peeling, and bleeding of the lips; a strawberry tongue; and diffuse erythema of the oropharyngeal mucosa), changes in extremities (erythema and firm edema of the dorsal aspects of the hands and feet with stretched and shiny skin; sharp demarcation at the ankles and wrists with an abrupt change to healthy skin; periungual desquamation), and cervical lymphadenopathy (usually unilateral, firm, non fluctuant, variably tender, and confined to the anterior cervical triangle; no overlying erythema) [105, 106].

Roseola-like erythema induced by intranasal buserelin, a gonadotrophin-releasing hormone agonist, has been reported [107]. The eruption was not associated with fever and subsided two weeks after the medication was discontinued [107].

6. LABORATORY STUDIES

Given the benign and self-limited nature of classical roseola infantum, laboratory investigations are usually not necessary. Children with roseola infantum may have sterile pyuria, and in one study, 21 (13%) of 158 children with roseola infantum were found to have sterile pyuria [72]. In the pre-eruptive phase, a urinalysis and urine culture should be considered if a urinary tract infection is suspected. Occasionally, children with roseola infantum may have transient neutropenia and thrombocytopenia. A complete blood cell count is not necessary unless clinically indicated.

Serological tests, including immunofluorescent antibody assays, enzyme immunoassays (EIA), immunoblot assays, virus-neutralizing antibodies to demonstrate seroconversion of anti-HHV IgM or ≥ fourfold rise in anti-HHV IgG, virus culture, polymerase chain reaction (PCR) assays to detect viral DNA in body fluids and tissues, and reverse transcription PCR (RT-PCR) can be used to diagnose HHV-6 and -7 infections [12, 108-111]. Virologic studies may be considered in patients with atypical presentations or complications and immunocompromised patients. These tests are usually restricted to research laboratories.

7. COMPLICATIONS

Febrile seizures occur in approximately 10 to 15% of children 6 to 18 months of age with roseola infantum during the pre-eruptive stage of the illness, especially on the first day of the fever [112-117]. It has also been observed that febrile seizures occur mainly during the febrile phase of the illness, especially on the first day of the fever [112-116]. Seizures may be related to the fever per se, or they may result from the direct viral invasion of the central nervous system [112-114]. Occasionally, HHV-6 and HHV-7 have been detected in the cerebrospinal fluid of children with roseola infantum [118-121]. It has been shown that some infants with roseola infantum have high serum levels of matrix metalloproteinase 9 and tissue inhibitor of metalloproteinase 1, which may impair the blood-brain barrier and lower the threshold for febrile seizures [122]. Febrile seizures, which may occasionally lead to status epilepticus, are the most common reason for hospitalization in children with roseola infantum [12].

Thrombocytopenia is an uncommon but known complication of roseola infantum [23, 123]. This complication can often go unrecognized because thrombocytopenia is relatively mild and occurs in the late phases of the illness [124]. During the recent COVID-19 pandemic, some children with roseola infantum were found to have transient leukopenia, severe neutropenia, and thrombocytopenia, the exact cause of which is not known [125]. In a study involving seven children with roseola infantum who were found to be HHV-6 positive by PCR, Aktürk *et al.* found that four of these children had transient leukopenia, severe neutropenia, and thrombocytopenia [125]. None of the children had COVID-19, and the cause of the hematological disturbance was otherwise unexplained. It has been observed that thrombocytopenic purpura may result if the platelet count is low enough.

In general, serious complications are rare and occur more often in individuals who are immunocompromised. Rarely, invasion of the central nervous system by HHV-6 or HHV-7 may lead to aseptic meningitis, encephalitis, encephalopathy, brainstem infarction, hemiparesis, and inappropriate antidiuretic hormone secretion [126-136]. For some unknown reason, encephalitis and encephalopathy are more commonly seen in infants in Japan [12, 137]. It is estimated that approximately 62 cases of exanthem subitum-associated encephalitis occur in Japan every year [137]. There is also an increased risk of epilepsy, chronic fatigue syndrome, and multiple sclerosis later in life [138, 139]. Other rare complications include mononucleosis, pneumonia, myocarditis, hepatitis/fulminant hepatic failure, rhabdomyolysis, and Guillain-Barré syndrome [7, 12, 38, 79, 123, 140-142].

8. MANAGEMENT

There is no specific treatment for roseola infantum. An antipyretic may be used to reduce fever and discomfort. Supportive care consisting of rest and maintaining fluid intake is advisable. Early recognition and treatment of complications, such as rare neurological complications, may help to prevent adverse outcomes.

Good personal hygiene is important as the virus is shed in the respiratory droplets and saliva. Good hand-washing habits, avoidance of close contact with infected individuals, and sharing of personal items should be encouraged.

9. PROGNOSIS

Roseola infantum is generally a benign and self-limited disease. Most children recover without sequelae. Recurrences of roseola infantum are not uncommon. The prognosis is excellent in most cases. Cases complicated by neurological involvement, such as encephalitis and encephalopathy, however, may have a poor outcome with significant neurological sequelae [79, 137].

CONCLUSION

Roseola infantum is a common childhood viral illness. While the majority of cases are benign, the condition may be complicated by febrile seizures and, occasionally, aseptic meningitis, encephalitis, and other neurological sequelae. Failure to recognize this condition may result in undue parental fear, unnecessary investigations, delay in treatment for conditions that mimic roseola infantum and complications that may arise from roseola infantum that need to be treated, unnecessary treatment of roseola infantum per se, and misuse of healthcare expenditure.

AUTHORS' CONTRIBUTIONS

Professor Alexander K.C. Leung is the principal author. Dr. Joseph M. Lam, Dr. Benjamin Barankin, Dr. Kin Fon Leong and Professor Kam Lun Hon are coauthors. All the authors contributed to drafting and revising the manuscript and approved the final version submitted for publication.

LIST OF ABBREVIATIONS

DNA = Deoxyribonucleic Acid

EIA = Enzyme Immunoassays

HHV = Human Herpesvirus

PCR = Polymerase Chain Reaction

RT = Reverse Transcription

CONSENT FOR PUBLICATION

Verbal consent was taken from the parents to publish the images.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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