CLINICAL IMAGES

Febrile Exanthem

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A 13-month-old black female presented to her family practice office with a four-day history of fever, nasal congestion, and loose stools. Her maximum temperature was 103.9 degrees Fahrenheit, obtained rectally. Symptoms accompanying the fever included diminished appetite, irritability, and malaise. The child is otherwise healthy and up-to-date on immunizations. She resides at home with her parents and was enrolled in daycare one month ago. On the fifth day of the illness, the child's fever subsided. She then developed an erythematous maculopapular rash restricted to the trunk, sparing the palms, soles, and oral mucosa.

FIGURE 1:
Frontal abdominal view

FIGURE 2:
Lateral flank view

QUESTIONS:

What is the most likely diagnosis?

a) Kawasaki disease
b) Measles
c) Roseola
d) Rubella
e) Scarlet fever

What is the primary viral culprit of roseola?

a) HSV-1
b) HHV-3
c) HHV-4
d) HHV-5
e) HHV-6

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ANSWERS

What is the most likely diagnosis?

The correct answer is:

C) Roseola

Roseola is a benign, self-limited virus caused by HHV-6 that typically presents as fevers between 102 and 105°F (38.9–40.6°C) followed by defervescence and subsequent development of a diffuse maculopapular rash.[1,2] The differential diagnosis of roseola consists of measles, rubella, scarlet fever, enteroviruses, adenoviruses, Epstein-Barr virus, and Kawasaki disease.[1,2] The measles virus is characterized by fever, cough, coryza, conjunctivitis, Koplik's spots (white spots on the buccal mucosa) and an erythematous maculopapular rash that classically starts on the face and spreads to the trunk, arms, and legs.[3] Rubella presents with a macular rash spreading from the head to the trunk, arms, and legs, accompanied by mild fever, malaise, posterior lymphadenopathy, and arthralgia.[4] Kawasaki disease is a common pediatric vasculitis characterized by a fever of at least five days plus four of the following: bilateral conjunctival injection, oropharyngeal erythema with fissuring of the lips and strawberry tongue, erythema and edema of the hands and feet with periungual desquamation, an erythematous rash, and cervical lymph node enlargement to >1.5 cm in diameter.[5] Scarlet fever is a bacterial exanthem that follows infection with streptococcal pyrogenic exotoxins from tonsillitis or pharyngitis.[2] A sore throat, high fever, headache, malaise, chills, and anorexia precedes the de-velopment of a sandpaper-like rash by 12-48 hours that spreads from the neck, chest, and axillae down to the trunk and extremities.[2]

What is the primary viral culprit of roseola?

The correct answer is:

e) HHV-6

HSV-1, Herpes Simplex Virus 1, causes an orolabial herpetic infection, otherwise known as cold sores.[1,2] HHV-3, Varicella Zoster Virus (a vesicular viral exanthem), causes chickenpox, and when reactivated, Herpes Zoster.[2,6] HHV-4, Epstein-Barr Virus, causes infectious mononucleosis.[2,7] It is also associated with lymphoproliferative disorders.[2,7] HHV-5, cytomegalovirus, is a member of the group of TORCH infections and can cause congenital deafness and mental retardation.[2,6] HHV-6 is the virus that causes roseola.

DISCUSSION

Roseola infantum, also referred to as exanthema subitum and sixth disease, is a clinical syndrome detected in early infancy and childhood primarily caused by infection with Human herpes virus 6 of the subfamily betaherpesvirinae and genus Roseolovirus.[1,2] While HHV6 is the most common cause, in 1994 HHV7 was also discovered to be a second culprit.[8] Both infect lymphocytes, have a predilection for T cells and can establish lifelong latency in these cells. The virus commonly infects infants and children between the ages of six months and three years and targets males and females equally.[9,10] Epidemics tend to have an incubation period of 9-10 days and the transmission of roseola occurs via infectious respiratory secretions, such as saliva.[2,5,8]

The diagnosis of roseola is predominantly clinical, revealed by the classic pattern of a 3-5 day fever, defervescence and subsequent development of a viral exanthem in a well appearing child.[1,7,9] The rash, which typically originates on the trunk and spreads peripherally to the extremities, is small, blanchable, generally non-pruritic rose-pink macules and maculopapules that are 2-5 mm in diameter with a peripheral halo of vasoconstriction.[1,2,5,7,9,11] Periorbital edema, cervical lymphadenopathy, and upper respiratory tract infection, when present, often mark the preexanthematous stage.[1,5,7] The exanthem itself appears asymptomatically and either lasts 1-2 days or occasionally persists for 2-4 hours.[1,7,12] Mild coryza, headache, and abdominal pain may also be present in the clinical history.[1,7,12] As the disease progresses, two-thirds of patients may develop Nagayama spots, erythematous papules localized to the mucosa of the soft palate and uvula.[1,2,7] One study examined 176 infants with an established diagnosis of exanthem subitum and confirmed infection with HHV-6.12 that 98 % of subjects had a fever, 98 % had a macular or papular rash, 68 % had mild diarrhea, 30 % had edematous eyelids, 65 % showed erythematous papules in the pharynx, 50 % had a cough, 31 % developed cervical lymph node swelling, 26 % showed swelling of the anterior fontanelle, and 8% had convulsions.[12]

While lab values are not typically used for the diagnosis of roseola, the gold standard for diagnosis of an HHV-6 infection is laboratory evidence of seroconversion in paired sera with a rise in anti-HHV IgM demonstrated in serum samples during the first week and conversion to anti-HHV IgG two weeks later.[2,8]

The differential diagnosis for roseola includes, but is not limited to measles, scarlet fever, Epstein-Barr virus, rubella, and Kawasaki disease.[1,2] Measles rash typically begins on the face or mouth (in the form of Koplik spots) and spreads cephalocaudally or centrifugally to reach the neck, trunk and extremities.[11] Children with measles appear more ill than those with roseola.[11] Scarlet fever is a condition diagnosed in 10% of cases of streptococcal tonsillopharyngitis marked by fever and sore throat, preceding a rash of sandpaper-like papules that starts on the trunk and spreads throughout the body.[11] In scarlet fever the palms and soles are spared, a circumoral pallor is observed, and the rash develops slowly.[11] Pastia lines, red non-blanching linear rash that appears in skinfolds, distinguish it from other rashes.[11] EBV-induced mononucleosis can also produce a rash, but it is typically associated with exudative tonsillitis, a hyperemic oropharynx, and palatal petechiae.[2] While it may resemble other exanthems, the rash associated with EBV often follows the ingestion of amoxicillin in a patient suspected of having strep throat.[13] The macular rash associated with rubella spreads caudally and involves lymphadenopathy of the posterior cervical, suboccipital, and posterior auricular lymph nodes.[2] Kawasaki disease, a rare cause of pediatric rash, presents as a polymorphic exanthem coupled with mucocutaneous findings and is a clinical diagnosis.[2] Diagnostic criteria for Kawasaki disease include fever for a minimum of five days in addition to four of the following characteristic features: bilateral conjunctival injection, a polymorphous rash, changes in the mucous membranes of the oral cavity (such as fissuring of the lips or strawberry tongue), changes in the peripheral extremities, cervical lymphadenopathy of greater than or equal to 1.5 cm in diameter, and exclusion of diseases that present with similar manifestations.[4]

Roseola is generally a benign, self-limited illness with an uncomplicated course, requiring symptomatic treatment.[10] Antipyretics such as acetaminophen or ibuprofen can be administered to relieve the fever.[3,5,10] Immunosuppressed patients are more susceptible than the general population to reactivation of HHV-6 and HHV-7, the major viruses that cause roseola.[8] A more severe clinical course can follow viral reactivation, which may be marked by rare, yet serious sequelae such as encephalitis, meningitis, multiple sclerosis, myocarditis, chronic fatigue syndrome, giant cell hepatitis, and pneumonitis.[8] Immunocompromised patients may be treated with antiviral therapy to avoid a more deleterious clinical course, but no randomized clinical trials exist to validate a recommendation on this.[2,14] Since the viral sensitivity profile of HHV-6 bears striking similarity to that of CMV, ganciclovir and foscarnet can be used for such cases, but specific treatments are still being studied.[7,14] Febrile seizures, which constitute the most prevalent complication of roseola, occur 10-15 percent of the time.[2,5,7]

This patient's symptoms resolved after several days. Her four-day fever followed by a maculopapular rash migrating from the trunk to the proximal extremities is consistent with a typical clinical presentation of roseola. She was treated symptomatically. The patient did not suffer any known complications and had no scarring from the rash. When considering roseola as a diagnosis, the clinician should always maintain a high clinical suspicion for other pediatric rashes of more serious etiologies. The challenge faced by physicians in the future will be to engage in discussion with patients about the viral etiology of roseola and to curb misuse of antibiotics.

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REFERENCES:

1. Paller A, Mancini A. Hurwitz Clinical Pediatric Dermatology: A Textbook of Skin Disorders of Childhood and Adolescence. 5th ed. 2016; 16:382-401.
2. Bolognia J, Jorizzo J, and Schaffer J. Dermatology. 3rd ed. 2012; 80:1321-1343, 81:1345-1365.
3. Habif T. Exanthems and drug eruptions. In: Clinical Dermatology. 3rd ed. 2016; 14:534-576.
4. Cherry, J. Human herpe sviruses 6, 7, and 8. In: Feigin and Cherry's Textbook of Pediatric Infectious Diseases. 7th ed. 2014; 77:1064-1085,160:2016-2021.
5. Kimberlin D, Brady M, Jackson M, Long S. Red Book: 2015 Report of the Committee on Infectious Diseases. 30th ed. 2015; 3:449-453,494-500.
6. Goldman L, Schafer A. Varicella-zoster virus (chickenpox, shingles). Goldman-Cecil Medicine. 25th ed. 2016; 375:2227-2229.
7. Mandell G. Viral diseases. In Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 6th ed. 2005; 1731,1772-1777.
8. Stone R, Micali G, Schwartz R. Roseola infantum and its causal human herpes viruses. International Journal of Dermatology 2014; 53:397-403.
9. Stockman J, Oski FA. Exanthem subitum. In: Yearbook of Pediatrics 1990; 46-49.
10. Hurwitz S. Exanthem subitum. In: The Pediatric Clinics of North America 1991; 860,867-868.
11. Allmon A, Deane K, and Martin K. Common skin rashes in children. In: American Family Physician. 2015;92(3):211-216.
12. Yoshizo A, Yoshikawa T, Suga S, *et al*. Clinical features of infants with primary human herpesvirus 6 infection (exanthem subitum, roseola infantum). Pediatrics. 1994; 93:104-108.
13. Di Lernia V, Mansouri Y. Epstein-Barr virus and skin manifestations in childhood. International Journal of Dermatology. 2013;52(10):1177-84
14. Schlossberg D. Human herpes viruses 6, 7, and 8. Clinical Infectious Disease. 1st ed. 2008; 186:1281-1284.