



Fever and Rash Syndrome: A review of clinical practice guidelines in the differential diagnosis

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ARTICLE INFO

Article type:

Review Article

Article history:

Received: 15 April 2013

Revised: 23 June 2013

Accepted: 12 July 2013

Keywords:

Fever, Rash, Syndrome,
Narrative Review

<http://jpr.mazums.ac.ir>

ABSTRACT

Fever accompanied by rash is a common finding in pediatric patients. Although, in most cases, the disease is trivial, in some cases it may be the first and/or the sole manifestation of a serious and life-threatening condition in patients. The spectrum of differential diagnosis is broad and many different infectious and some noninfectious agents cause this syndrome. To establish a timely diagnosis, providing appropriate therapy and considering proper preventive measures if necessary, a systematic approach relying on a clear history, careful clinical examination along with particular attention to epidemiological features are the most important factors to pursue this syndrome. In this paper, the aim is to give an overview of how to deal with these patients clinically to establish a timely probable diagnosis of patients, providing proper early medical intervention without applying specific laboratory tests.

Introduction

Fever and rash is a common clinical complaint in patients presenting to physician office and emergency department. The syndrome causes anxiety in both the parents and physicians. The causes are many and the ranges of differential diagnosis are very wide and contained a large number of infectious and noninfectious illnesses. Although in the majority, the disease

is benign and self-limited, sometimes, it may be the first or the only sign of a serious and life-threatening condition. Therefore, to provide an immediate appropriate medical intervention, early clinical diagnosis is necessary. In the initial evaluation of a febrile child with rash, a proper history and careful clinical examination is essential rather than relying on laboratory

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tests which results may not be immediately available. In most cases, a systematic approach based on tripod of clear history, careful clinical examination with the special attention to the types and other characteristics of rash and their relation to fever and other signs and symptoms, along with the properly targeted epidemiological clues can aid to establish possible diagnosis and select those patients who need immediate medical intervention without applying specific laboratory tests.¹⁻⁴

In this paper, our aim was to review a proper clinical diagnostic approach without applying special laboratory tests to diagnose timely those patients who require immediate medical intervention relying on the history, physical examination and the epidemiological clues. In addition, at the end of the paper, a short overview has been done on number of diseases with fever and rash that their early diagnosis and appropriate therapeutic intervention are considered as medical emergencies.

A. Clinical examination.

In the initial evaluation of the febrile child with rash, certain factors must be given urgent priority, these include:

a: Is the patient well enough to be evaluated on as outpatient setting or needs hospitalization?

b: If admission is required, is the patient's life threatened from the disease and an urgent medical intervention required?

c: Is there the risk of transmission to others and warranted precaution and isolation?

d: Does the disease acquire notification from the public health point of view?

Careful clinical examination is essential in any patient presenting with fever and rash. Special attention to the general appearance; hemodynamic and respiratory status and consciousness level to select the minority patients at risk are very important of life saving. Full examination of skin and mucosa is very important to determine the characteristics of rash (eruption sites, distribution, progression

and evolution), searching for signs of meningeal irritation (Kernig's and Brudzinsky signs) with neurological examination, assessment of hepatomegaly, splenomegaly, lymph nodes and other parts of the body are essential to diagnose and differential diagnosis of the disease.

B. Types and characteristics of skin rash:

Various infectious and noninfectious agents can cause different skin reactions and/ or similar clinical syndromes or vice versa. In evaluating a patient with fever and rash, determining the type of rash, and its general characteristics such as the primary site of eruption and progression to the other parts of the body, their distribution and the evolution are very important.

Dermal manifestations and various kinds of rash can be categorized based on the form of rash (macular, papular, vesicular, blistery, petechial and purpuric) or according to the general term of a disease with rash overall known as measles-like rash "Morbiliforme"; like rubella " Rubelliforme "; or similar scarlet fever " Scarlatiniforme = scarlet-fever like illness"; and so on. In addition, considering the distribution of rash throughout the body (diffused or localized rash, symmetrical bilateral or unilateral, at open or shaded areas), and how to distribute from the primary site to other parts of the body (central: the bulk density on the face, trunk, and abdomen or peripheral area: the highest density on the extremities) will be useful to distinguish the pathogens from each other.^{1, 3-5} The following definitions are useful to describe the various types of rash.⁵

Macula: A color change of the skin, **Papules:**

A raised lesion less than 1 cm in diameter,

Maculopapular: A combination of both macules and papules, **Purpura:**

Cutaneous lesions caused by leakage of red blood cells, may be/not be palpable with a diameter more than 5 mm and **petechia:**

is a similar lesion smaller than 5 mm diameter, **Vesicle:** is a blister like lesions less than 1 cm diameter containing

fluid and the larger lesion is called **Bullae:**

Pustule: a pus-containing vesicles, that may leave scar after healing, **Enanthem:** A mucosal rash on the mucous membranes, sometimes mucosal rash (Enanthem) is a specific sign of a disease like **Koplik spots** in measles, petechial lesion on soft palate in rubella, and infectious mononucleosis, anterior oral vesicolo-ulcerative lesions in Hand- Foot- Mouth disease.

C. Determination of the relationship between fever, rash and other clinical symptoms:

Consideration and determining the correct relationship between fever and rash and also other signs/ symptoms are the crucial points to differentiate between febrile illnesses accompanied by rash.^{1, 3- 5} In evaluating a patient who is suffering from fever and rash syndrome, accurate answers to the following questions will be helpful in the diagnosis of the disease:⁵

- ❑ **What is the shape and type of rash?**
- ❑ **When and where the rash started?**
- ❑ **Has the rash progressed to other parts of the body?**
- ❑ **What is the relationship between fever and rash?**
- ❑ **Has the rash changed morphologically?**
- ❑ **Were there any other signs/ symptoms before the rash erupted?**
- ❑ **Has treatment begun for the patient?**

For example: **Measles:** An acute viral exanthematous illness that begins with malaise, fever, cough, runny nose and conjunctivitis that becomes more severe within 3-4 days later.⁶

About 12- 48 hours before the onset of rash, measles-specific enanthem appears in the anterior aspects of the cheeks and gums at the levels of premolar may spread and involve the lip, hard palate and gingiva, opposite the maxillary second molars on a red halo with a bluish-white central dot (Koplik spots). At the peak of fever and other clinical symptoms of measles, red color maculopapular lesions erupt from the back and anterior of the ears from the

hairline and progress to the other parts of the body and extremities. The concentration of rash in the trunk and abdomen is much higher than in the limbs. This kind of distribution of the rash to the body and its clinical picture is called «Morbilliforme Rash». Fever and other signs/ symptoms lasted for 48 hours after rash eruption and were resolved suddenly, in which the patients' general conditions improved significantly. On the fourth day of the rash eruption, gradual disappearance of the rash with fine desquamation begins from the face and spreads to the extremities within several days. Measles-like rash has no or a little pruritus.⁷ The epidemiological trend of measles changes significantly following universal vaccination of children against measles. In most countries, the incidence of measles was markedly reduced and endemic measles was eliminated in some parts of the world. In these countries, majority of the cases occur among infants, adolescents and young people. In Iran, since 1989, after a two-dose of routine mass vaccination against measles in children ages 9 and 15 months with high coverage levels, cases of measles in children have decreased significantly and the most reported cases of measles have been in older children and adults.^{7, 8} Considering the changes in the epidemiology of measles in Iran and around the world, in the differential diagnosis of febrile diseases with rash, measles is also considered in adolescents, young adults and infants.

Rubella: An acute mild exanthematous viral disease with least morbidity in children, which clinically is similar to the mild measles (also called three-day measles).⁹ Infection in pregnancy may result in fetal infection and considerable fetal developmental anomalies. The rash of the disease may be presented 1- 3 days after a mild systemic symptoms such as low-grade fever (less than 38.5 ° C), cough and runny nose. Rubella rash starts on the face of

the patient. The type of rash in rubella is a red maculopapular that initially appears on the face and spreads to the extremities in less than 48 hours. The most concentration of rash appears on the face and trunk with discrete lesions in the extremities. As a view point of clinical feature, such spreading of rash on the body is called «Rubelliforme Rash». The main characteristic of the disease is severe painful lymphadenopathy behind the head or behind of the ears that present before the rash eruption and remains for a week. In some cases, a few enantheams may be presented like a petechia on the soft palate.⁹ Diagnosis of rubella is important to prevent transmission of the infection to pregnant women. Acquiring rubella infection in the first few months of pregnancy is associated with severe complications in the fetus and the risk of congenital rubella syndrome. In some areas of the world where rubella vaccination is not carried out, rubella is a childhood disease; affecting children and adolescents in the age groups of 5-15 years. In these areas, most girls and women in childbearing age, following normal exposure to the infection have acquired immunity, so that, in the reproductive age if once exposed to the patient infected with rubella, the risk of infection is very low.¹⁰ In faced to a pregnant woman exposed to a febrile patient with rash confirmed or suspected to rubella, immediately testing for rubella specific IgG antibodies should be performed. If the test result is positive, it means that the pregnant woman is immune and her fetus is not threatened.

Roseola: "Exanthem Subitum"; An acute febrile disease is caused by the human herpes viruses 6 and 7.¹¹ The sudden onset of high fever, malaise, and sometimes seizures without other significant clinical signs/ symptoms in 3-36 months old children with nontoxic appearance will occur. The most important characteristic of the disease is a reddish maculopapular rash without pruritus on the

trunk, neck, sometimes on the face and the proximal part of the arms that appear within a few hours after a sudden fever lysis. In some cases, adenopathy in the postauricular – occipital area can be detected. Because of the special relationship between the fever and the rash eruption, clinical diagnosis of the disease is simply possible and less confused with other febrile diseases with rash.¹¹

Parvovirus B19 Infection "Erythema Infectiosum": Infection results in a wide spectrum of clinical presentations. Usual clinical manifestations of the disease mainly occur in children and have three distinct stages: The **first stage** begins with nonspecific symptoms such as headache, malaise, mild fever, cough and mild runny nose for 2-3 days. One week later, the first exanthematous phase of illness starts with a raised fiery red rash appearing on the cheeks of the patient like a "Slapped- Cheek" and with circumoral Pallor. The lesions are aggravated with exposure to the heat. The **second phase** of enanthem starts 1-4 days after the facial rash with the development of a maculopapular rash on the trunk and extremities that initially are discreted and gradually spread to involve all parts of the body. Several days after the appearance of the rash, the central part of the lesions gradually is cleared and lesions extended peripherally and make a reticular appearance that is the beginning of **third stage** of the disease. This stage last for 1-3 weeks. After the rash has disappeared, frequent recurrency may occur following exercise or heat exposure. The major parts of the body that rash can present in the third stage are the extensor surfaces of extremities without the involvement of the palms and sole. Rash is pruritic but no desquamation occurs.¹²

Scarlet Fever: An acute infection that is caused by Strep group A. In most cases, the disease is observed in children ages 5-15 years, which starts with a sudden high fever, sore throat,

abdominal pain and vomiting. Physical examination reveals pharyngitis with / without exudates, and painful submandibular adenitis. 12- 48 hours after the onset of the disease, erythematous macular rash appears on the patient's face (Slapped- cheek) with circumoral pallor, and also a red maculopapular rash on the trunk and abdomen that in some cases within several hours spread to all parts of the body. Although the rash may fade with pressure in the different parts of the body but in the wrinkles of elbow and wrist become more colored "known as Pastia line / sign." On the throat, in addition to the evidence of pharyngitis, enanthem of the disease can be seen as petechic spots on the soft palate and anterior pillar of the tonsils. Smooth desquamation, especially on fingertips occurs in all patients that last for 1-3 weeks.¹³

Infectious Mononucleosis: The disease is caused by Epstein - Barr virus. One week before the onset of the main symptoms of the disease, there are general malaise, fatigue, and mild fever in the patient. The common characteristics of the disease are manifested by high fever 38.5 – 40.5° C for 1-2 weeks, pharyngitis; mostly with white membrane, and cervical lymph node enlargement. Splenomegally occurs in one-third or half of the patients. A few days after the onset of typical symptoms of the disease, a red maculopapular rash appears on the trunk in 10-15% of the patients. Also, 5-7 days after the administration of ampicillin or beta-lactam antibiotics to the patients with infectious mononucleosis, a red maculopapular rash without pruritus appears on the trunk, face and extremities.¹⁴

Kawasaki Disease (KD): KD is an unknown etiologic febrile disease with rash. The diagnostic criteria of the disease are based on clinical evidences including; a fever lasting more than 5 days associated with four out of the five following symptoms: bilateral non-purulent severe redness of conjunctiva,

especially without the involvement of limb, redness and inflammation of the oral mucosa (strawberry tongue , redness and transverse cracking and bleeding of the lips, inflammation of the pharynx and oral mucosa together or separately), multiform skin rash especially a red maculopapular rash most notably occurs on the trunk or redness in the perineum area with desquamation, red indurated - painful stiffness of extremities in the acute phase and/or large and huge desquamation of nail bed from the second week and ultimately cervical adenopathy more than 1.5 cm anterior to the neck without redness with mild pain. In the usual case of the disease, diagnosis is not a problem.¹⁵

Enterovirus infections: Enterovirus infections manifest with a variety of muco-cutaneous rash. One of the characteristics of the clinical syndrome due to enterovirus infections is Hand-Foot- Mouth disease which is associated with fever and vesicular lesions in the distal parts of the limbs, wrists and the anterior area of mouth that are not "crusted". Another clinical syndrome caused by enterovirus infection is Herpangina. In this disease, vesicular lesion 2-4 mm in diameter occurs into the mouth, especially on the soft palate. In some clinical syndromes and infections caused by ECHO viruses, fever and petechic-purpuric type of rash may occur. Also, many enterovirus species are able to create fever with maculopapular rash on the trunk. With regard to the different clinical syndromes of fever with rash resulting from enterovirus infections, the majority of the above mentioned infections are in the differential diagnosis of febrile illness with rash. The most epidemiologic features of enterovirus infections are that they most commonly occur during the summer and autumn seasons. In this period, a variety of clinical syndromes may be observed in the community.¹⁶

Chickenpox: An acute viral disease that is characterized by extremely itchy small vesicles. Usually, after 12-24 hours of fever and malaise, cumulative and sudden skin rash known as "crop" begins to erupt on the scalp, face and trunk. There are various types of skin lesions from macula up to crusted lesion at different anatomical regions on physical examination. There is a red halo around the lesion. The lesion is umbilicated. The distribution of rash is centric and the most concentration of rash is on the face, trunk and abdomen. Also, lesions of chickenpox occur in the various mucosa of the body. In cases of localized vesicular lesions, herpetic lesions, zoster, bites and poison ivy should be considered.¹⁷

D. Epidemiological Features and Etiology:

The relative role of each pathogen is not the same in different regions or different individuals. Information about the relationship between patient and a pathogen and their environments is a very important point when faced with a patient with fever and rash syndrome (FRS). If the epidemiology of the different agents is well understood and used, it will be very helpful to differentiate between a pathogen from other causes of similar clinical syndrome. The epidemiologic characteristics that require special attention are: patient age; geographic region; season; history of travel to other location; contact with insects, animals, food or plants and similar patients; history of vaccination and history of prior illness; the immune status of host and medications.⁵

1. Age of the patient: Some diseases that are presented with rash especially "viral diseases" mainly occur in childhood. Considering the age of the patient can help to narrow the range of differential diagnosis of the diseases.

Roseola infantum is an infection mostly occurs in children 3-36 months of age.¹¹ Erythema infectiosum also known as "Fifth disease" is referred to the clinical manifestations of Parovirus B-19 (PB-19) infection. The classic

illness is manifested in children. However, in older children, less commonly disease is presented with skin rash.¹² Kawasaki disease is an acute unknown etiology childhood illness with skin rash.¹⁵ Scarlet fever and infectious mononeuclosis are the two diseases among the pediatric patients aged 5-15 years caused by strep A and Epstein-Barr viruses, respectively.^{9,14} Enterovirus infections associated with rash mainly occur in infant and younger children.¹⁶ In the past, some viral diseases preventable by vaccination such as measles⁷, rubella⁹ and chickenpox¹⁷ were childhood diseases. With the universal routine vaccination against the above mentioned viral infections and changing the epidemiological trend of the disease, more cases occur in adolescents and young adults which should be considered.

2. Season of the year: A large number of infectious agents that are associated with fever and rash have specific seasonal activity. Considering the seasonal activity of the pathogens can assist the physician in restricting the differential diagnosis of FRS. For example, the peak activities of enterovirus species occur in the summer and autumn¹⁶, Measles⁶ and Rubella⁹ present in the spring, parvovirus B19¹² and meningococcal bacteria¹⁸ occur in the winter and early spring, and Tick-borne diseases such as Lyme diseases, Rickettsia infection and Rocky Mountains spotted fever (RMSF) may also occur in the summer.^{19,20}

3. Geographic area: Some pathogens or their carriers can survive or are active in special climates. As a result, some of the diseases are observed or limited to some particular geographic regions. Staying or traveling to these areas are likely to be associated with the risk of acquiring the diseases. For example, RMSF or Lyme disease^{19,20} are active in some areas of America or dengue fever and dengue hemorrhagic fever are also active in South East Asia.²¹ Traveling to some areas like South

Africa, India, Russia and the Mediterranean countries is associated with the risk of rickettsiae conori infection.¹⁹ There is a risk of infection to a number of other rickettsial diseases such as Rickettsial Pox and Boutonuse fever among the travelers from other parts of the world such as China, India, Nepal, the Mediterranean countries and Russia (Table 1).^{19, 20} People who travel to India, Pakistan or Mexico are at risk of exposure to Typhoid Fever.^{22, 23}

4. Incubation period: The history of contact with a known exanthematous infections, the interval from exposure to rash onset of the disease (incubation period) can help the physician to identify the pathogen. For example, an interval of 14 days from exposure to onset of rash suggests measles⁶ 18-21 days for rubella, 14-18 days for chickenpox¹⁷, and 4-

7 days suggest enterovirus infections.¹⁶ Sometimes the interval between the bite and expression of the symptoms will be the key in differential diagnoses, like 14-17 days interval between tick bites and presence of skin lesion in Lyme disease or in RMSF.^{19, 20}

5. Exposure History: There are a variety of infectious agents around our non-living and living environments. There is a risk of acquisition of disease following professional or non-occupational exposure to the etiologic agents. Exposure to animals, food, plants and other patients are the most remarkable points in the differential diagnosis of the diseases with fever and rash. For example, there is a possibility of being infected by direct contact with the skin and mucous membrane of the infected people with HSV, syphilis, gonorrhea and HIV.

Table1. Summary of characteristics of the different types of Rickettsia

Type of disease	Geological region	Incubation period (day)	Onset of rash following fever	Type of rash and kind of distribution	Other signs & symptoms
Boutonuse fever	Southern Europe and the Middle East, Russia, India and Pakistan	7-14 days	4-7 days	Maculopapular, trunk	Headache, malaise
Typhus groups	pandemic	7-15 days	5-7 days	Maculopapular and petechic, peripheral distribution without palms and soles involvement	Very severe and uncontrolled headache
Spotted groups	pandemic			Maculopapular and petechic, from peripheral to central parts	Headache, malaise, myalgia
Reckettisial pox	pandemic	9-14 days	4-7 days	Maculopapular and vesico-bollouse from peripheral to central parts without involvement of oral mucosa, palms and soles	headache

There is a probability of cat scratch disease and visceral larva migrans in contact with cats and dogs, leptospirosis and rat-bite fever likely follow contact with mouse, rodents and/ or cow and rickettsia or lyme disease may occur in contact with tick or mosquitoes. Contact with water, soil or plants may lead to some dermal and topical diseases.^{1, 4, 5}

6. Drug History: Various drugs can cause a variety of skin rashes that is sometimes accompanied by fever. Unlike the popular belief, association of fever and rash caused by drugs is not so common. For example, in a study, only 20% of patients with drug fever had skin rash that half of them were urticarial. In another study performed on 20,000 patients admitted to the hospitals, only 2% of the patients showed the drug induced rash, as most of them used antibiotics or anticonvulsant drugs for the treatment. Serious skin reaction of stevens - Johnson syndrome or toxic epidermal necrolysis "TEN" occurs in 5% of those affected patients. Drug-included skin reaction usually occurs about 1-3 weeks after treatment.^{1, 4, 5}

7. History of Vaccination and Immunization: Full vaccination against a disease or history of a natural infection is against the diagnosis of a particular infection. In the past, however in some cases, sometimes 1-3 weeks after vaccination, fever and/or rash related to live vaccine²⁵ or allergic reaction to vaccine component can occur. Considering the interval between the administration of the vaccine and the appearance of symptoms will be helpful in the differential diagnoses.^{1, 4, 5}

8. History of sexual activity: Every patient present fever and rash with unknown etiology should be evaluated carefully and in sexual activity. A thorough proper examination of the anogenital area is essential.^{2, 5} Human herpes (HSV1 and HSV2), syphilis, Chancroid are diseases which may be associated with localized rash in genital area or disseminated

throughout the body. For instance, a disease such as syphilis can cause a variety of rashes. Rash at the early stage of the disease may appear as painless ulcer with a raised red border, highlight color, and stiffer than the surrounding tissue. In the second stage of the disease, a red maculopapular rash distributed in all parts of the body including the palms and soles may occur. At this stage, in wet areas of the body, Condyloma-lata lesions especially in the anal area and mucosal ulcers of the mouth are observed. About 2-6 weeks after exposure to HIV, fever, headache, sore throat, diffused lymphadenopathy, mucosal ulcers, transient maculopapular rash without pruritus on the face and trunk areas are develop. The disease may not be differentiated with other diseases, especially infectious mononucleosis.^{1, 2, 5}

Laboratory Evaluation: Applying and using laboratory facilities are not much helpful to differential diagnosis of the diseases in patients suffering from fever with a rash, particularly in the early stages of the disease, and have a low diagnosis value in serious illnesses. However, in suitable conditions, the application of the following tests is recommended:

- Nonspecific tests such as complete blood count (CBC) and urinalysis
- Specific tests included: blood culture in specific media based on the condition of the patients, serological tests suitable for clinical and epidemiological conditions combined with antigen investigation in appropriate samples are more important. Fluid and discharge samples from the pustules, blister, vesicle, ulcerative lesions and petechic lesions prepared for culture and smear may be helpful to diagnosis the agent. Finally, microbiological and histological evaluation of skin biopsy may be useful for the diagnosis of the disease.¹⁻⁵

Some Diseases as Medical Emergencies:

Meningococcal Infections: Although gram-negative cocci of *Neisseria meningitidis* causes

a wide range of clinical conditions, the most important and the Life-Threatening clinical form of it is septicemia (Meningococemia). Meningococemia with / or without meningitis is a severe and life-threatening disease that frequently affects children and adolescents. The disease occurs more frequently in overcrowded conditions, such as barracks, dormitories, and kindergartens. Early diagnosis of the disease is a medical emergency because of the very rapid progression and high morbidity and mortality of the disease without early and proper treatment. The clinical manifestations of the disease include: fever, headache, myalgia, nausea, vomiting, and hypotension (shock). In some patients, loss of consciousness and signs of meningeal irritation (stiff neck, kernig and brudzinski signs) and concurrent skin rash are present in patients with Meningococemia. Initially, skin rash is a red maculopapular lesion on the trunk and limbs (without the involvement of the palms and soles) that will become petechic-purpuric within few hours. Due to rapid progression of the disease and possibly serious complications of delayed diagnosis, in any case with fever and petechic-purpuric skin rash with or without involvement of the central nervous system, to save a patient's life and to prevent the transmission of infection to others, an immediate appropriate special treatment of infection along with other control measures should be started against meningococemia and meningitis until it is ruled out or confirmed.^{18,}

²⁵⁻²⁷

Toxic Shock Syndrome: A known clinical syndrome that is caused by a toxin released from Staph, aureus and Strep A bacteria. Although, most cases occur in children, it may also occur in older children and women after the use of tampon, or in patients with burns, surgical wounds and from the skin lesion. The diagnosis of the disease in acute phase is based on clinical criteria including a fever more than

38.9 ° C, hypotension (shock) and diffuse erythema of the skin accompanied by three different organs involvement such as gastrointestinal tract, liver, kidney, nervous system, blood, and etc. Disease should be differentiated from illnesses such as leptospirosis, measles, Kawasaki, and rickettsial infections. The most common clinical manifestation of the disease are conjunctivitis, red mouth, diarrhea, vomiting, muscle pain, liver and kidney dysfunction, disseminated intravascular coagulopathy (DIC), thrombocytopenia, and impaired consciousness. In this patient, fever and rash (erythroderma) started together. To reduce morbidity and mortality, early diagnosis and appropriate supportive treatment with an immediate correction of the hypotension is essential.^{28, 29}

Staphylococcal Scalded Skin Syndrome: Reiter's disease (SSSS): The disease is caused by a toxin produced by staph aureus bacteria. Most cases of the disease occur in the first few months of life. The disease onset is acute with sudden high fever, restlessness, severe and extensive redness of skin (Tender erythroderma). The patient's skin is red, swollen and extremely painful that within 1-3 days, with a light pressure large thin-walled blisters will appear (positive Nikolsky sign) which can be easily torn. After tear off the blister, a red moisture surface appears that will change to a fine desquamation over the next few days. In uncomplicated cases, recovery occurs within two weeks. An early diagnosis and establishment of an appropriate specific treatment (anti-staphylococcal antibiotic) combined with fluid therapy and appropriate supportive treatment like those for burns is essential to reduce morbidity and mortality of the disease.^{28, 30}

Toxic Epidermal Necrolysis (TEN): Erythema multiform, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis TEN are actually a

syndrome with three different clinical presentations. Erythema multiforme is the milder form of the syndrome and very severe and dangerous form of it is called TEN. Many infectious and noninfectious agents are involved in the development of the disease. In most cases, Erythema multiforme usually occurs in burning older children and adults. There is burning and itching sensation before the onset of cutaneous lesions. The most important disease-specific lesion is «Target lesion» including a central lesion with discoloration and central necrosis with a normal skin in the margins. There is also a red color change again at the margin of normal skin. The primary central lesion starts as a red maculopapular or urticarial rash and rapidly evolves to central necrosis or may transform to vesiculobullous lesions. The distribution of lesions in the body is symmetrical and occurs at the extensor surface of the upper extremities (the least lesions are seen on face and lower extremities). The frequency and severity of these lesions are higher in Stevens - Johnson syndrome and involve about 30% of the body surface area (more lesions are seen on trunks and limb areas). In these patients, mucosal lesions in more than one mucous membrane (eyes, ears, nose, mouth, anogenital area, respiratory and gastrointestinal tract involvement) also occur. Burning sensation and swelling of the mucous membrane occur before lesions development. Redness, blister, ulcer and/or hemorrhagic crusting on lip, oral mucosa may develop. In a number of cases, fever and chills, pain, burning sensation of mucosa and skin can be seen before eruption of the skin rash. In cases of TEN syndrome, initially painful erythrodermi of the skin and then a very large, thin-walled blister occur. Target signs may not be present. Few to 48 hours before skin eruption fever and mucosal are present. In an uncomplicated case, recovery occurs within 10-14 days. There are various infectious and noninfectious agents

particularly drugs that have been responsible for causing the syndrome. Early diagnosis and prompt discontinuation of the responsible drug(s) in combination with supportive therapy similar to those of extensive burns associated with corticosteroid therapy and IVIG will be useful to reduce morbidity and mortality. The most important differential diagnoses of TEN are Reiter's disease (SSSS), pemphigus and toxic shock syndrome.^{1, 31, 32}

Rickettsial Infections and RMSF:

Rickettsiosis and RMSF is a set of vector-borne diseases that are transmitted from animals to humans by arthropods. (Table 1)

There are several common features such as sudden onset of high fever, various skin rash, damage to small vessels and capillaries, rapid progression to a severe and life-threatening disease, and presence of Eschar at the site of bite. With respect to the role of arthropod in transmission of microorganisms, these groups of diseases have a specific regional and seasonal incidence. The diagnosis was based on clinical and epidemiological evidences and measurement of specific antibodies or PCR. Immediate and empirical disease-specific treatment is essential to reduce or prevent the complications of the disease before specific diagnosis. RMSF is a tick borne Rickettsial infection and active in the defined geographical area in America. The incubation period of the disease is 4- 5 days. The onset of the disease is sudden with high fever, headache, general malaise, myalgia congestion and redness of the conjunctiva. 4-5 days after the onset of fever and initial symptoms of the disease, a red maculopapular skin rash appears on wrist and ankle areas of the body. The initial rash will be converted to pethectic- purpuric lesions in a short time. Over the next few days, the rash will be distributed and progressed downwards and upwards to the palms and soles and "arms and thighs respectively". In this phase, differentiation of the disease from

meningococemia is difficult. Residing in or history of travel to endemic areas, a history of tick bite, and attention to rash distribution and progression, the relation between rash and fever, accompanied with leukopenia, and increasing liver transaminase is helpful and beneficial for diagnosis of RMSF. The most important differential diagnosis of the disease is meningococemia. In addition, bacterial endocarditis, measles, second stage of syphilis, and other rickettsial diseases are also discussed. However, in the exposure to a patient with fever and purpuric rash, especially in endemic areas of the disease, immediate empirical disease-specific and supportive treatment is strongly recommended.^{19, 20, 33, 34}

Dengue Fever and Dengue Hemorrhagic

Fever: Is an acute viral disease transmitted by flies. Incubation period is 2-7 days. Although, it has been reported worldwide, but the majority of cases are reported from Southeast Asia.

Diseases begin suddenly with high fever, severe headache (most prominent on forehead and retro orbit), back pain, and lymphadenopathy. Within 24- 48 hours of fever, a temporary red maculopapular rash for 1-2 days develop. Bradycardia in proportion to fever is present. Musculoskeletal pain is very intense and intractable.

After 2-7 days, the clinical symptoms of the disease subside and the patient recovers temporarily. After 1-2 days of defeverness, a diffuse maculopapular measles-like rash appears without the involvement of the palms and soles.

In endemic areas, reinfection in people with previous history of the disease, or primary infection in infants and young children who have saved maternal antibody, the early symptoms of the disease are manifested abruptly by fever, headache and cough for 2-5 days and endured for 2-5 days. One to two days after the initial period, the general condition of

the patients will worsen and cardiovascular collapse and shock occurs. At this stage, the patient is restless and irritable with cold extremities and in some patients; diffused petechiae develop on the forehead and limbs. There are spontaneous ecchymosis and tendency to bleeding. Cyanosis, rapid and shallow breathing, weak and narrow pulse and short interval between systolic and diastolic phases of blood pressure, hepatomegaly, accumulation of fluid in the pleural cavity (pleurisy) can occur. This phase lasts for 24-36 hours. Establishing early diagnosis and appropriate supportive treatment is essential to reduce complications.^{21, 35, 36}

Conclusion

Fever associated with rash is a common clinical syndrome in patients presenting to physicians' offices and emergency departments. The causes are many and in most instances are benign and self-limited. However, in a small number of cases it may be the only sign of a severe and life-threatening or contagious infection.

The differential diagnosis of fever and rash is extremely broad, but systematic approaches could help clinicians for establishing a timely diagnosis, providing early treatment when appropriate and considering preventive measures if necessary.

In this regard careful physical examination, taking a clear history along with epidemiological clues is very important to pursue.

Conflict of Interest

None declared.

Funding/Support

None declared.

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