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"DERMADRISHTI"

Editorial Team :
Dr. Prabhakar. M. Sangolli
Dr. Praveen Kumar S

BANGALORE DERMATOLOGICAL SOCIETY
BANGALORE,KARNATAKA
www.bdsmembers.com

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President:
Dr. T.S. Vidya
Mob.: 9886352304
vidyaderma@gmail.com

Vice President:
Dr. Leelavathy B.
Mob.: 9448169982

Vice President:
Dr. T. S. Nagaraju
9902011525
drnagtalkad@yahoo.co.in

Secretary:
Dr. Nandini A. S.
Mob. : 9886829579
dmandinias2002@yahoo.co.in

Treasurer:
Dr. Praveen Kumar S.
Mob. : 9886320760
drpraveen.1982@gmail.com

Joint Secretary:
Dr. D.P. Jayanth
Mob : 9845310950

Joint Secretary:
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080-26664931

A note from the presidential desk:

We are happy to continue with the BDS newsletter-“DERMADRISHTI”, which covers all aspects of the activities of our Bangalore Dermatological society, a vibrant branch of the IADVL. This news letter is brought out quarterly by the editorial team comprising of Dr.Prabhakar M Sangolli and Dr. Praveen Kumar S. I wish all the success to this academic activity and request all the members of BDS to contribute actively to the journal. This is an opportunity for young dermatologists and postgraduates to showcase their talent.

I wish Dr. Sangolli and Dr. Praveen all the very best to take this journal to greater heights.

Dr. T. S. Vidya

President

Bangalore Dermatological Society

Presidential Message

It is with immense pleasure that I accepted the role of the President ship of Bangalore Dermatological society for the year 2015- 2017.

First of all let me thank, all my senior colleagues and all the members of the BDS for having trust in me to hold this prestigious post and also to host the academically mind boggling CME's, workshops, conferences, etc. I also thank all my colleagues and executive committee members for their support and encouragement.

To continue the good work of all my predecessors, I would like to enhance our goals.

Integrity

1. To enhance professional cohesiveness &to encourage the spirit of fraternity and the collegial spirit

Academics

3. To provide a platform for the up gradation of professional information, standards and skills
4. To guard and enhance professional and ethical standards of the members and thereby enhance the honor of the profession.

Digital

5. To make BDS completely paperless. All communication will be through mails, web site, messages, whatsapp and through other digital media.

Rural camps

6. To improve quality of life of people living in the rural areas through camps and awareness .

Memberships

7. The strength of any organization lies in the membership. So to see to it that every practicing dermatologist in Bangalore becomes a BDS member

CME's

8. To make every CME unique and worth the change.

Postgraduates

9. To encourage every PG student to participate , present cases and papers, compete, research and discuss and win laurels .

Women power

10. To encourage all women dermatologists to take up responsibilities in the social work.

Unique programs

11. To continue the tradition of introducing something unique in every term , eg. Capsules, Hand outs, Research grants etc .

Non dermatology talks

12. To introduce non dermatology talks for the benefit of all members, eg. investment, spirituality, fitness, etc to lead a better life

All this can be done only with the active participation, encouragement and support of all my team members, senior colleagues and the BDS fraternity .

I would like to thank all members for their continued co operation and to help me make BDS successful an important arm of IADVL.

Thank you and regards ,

Dr T S Vidya

President BDS

Message from the Secretary

I congratulate Dr Prabhakar Sangolli- our Past BDS president and a person know for his academic excellence and Dr Praveen Kumar S on bringing out the BDS NEWSLETTER, highlighting the activities and achievements of BDS. This should serve as an inspiration for those involved with BDS activities and as a motivation for those contemplating to be a part of the same and bring the best out of them.

Long live BDS

Dr. Nandini A. S.
BDS Secretary

Chief Editor's message

Bangalore Dermatological society-IADVL is always on the forefront as far as academic and socially relevant non- academic activities are concerned. Our BDS newsletter makes a honest effort to show case various achievements of BDS and its esteemed members.It contains review articles, conference summaries ,cartoons,quiz, information about various conferences etc.. I am grateful to Dr Praveen Kumar who actively designs and brings out the newsletter. I also thank our BDS President Dr Vidya TS and Secretary Dr Nandini AS for their encouragement.

I urge BDS members to contribute articles

Suggestions and feedback are welcome

Editorial Team

Dr Prabhakar M Sangolli

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FEVER WITH RASH IN CHILDREN

1. **Dr Sahana M Srinivas DNB, DVD, FRGUHS (Pediatric dermatology)**

Consultant Pediatric Dermatologist

Indira Gandhi Institute of Child Health, Bangalore

Sagar Hospital (Centre for Pediatric care), Bangalore

2. **Dr Payal Ranka MD**

Consultant Dermatologist

Cloud Nine Hospital, Bangalore

Introduction

Rashes may be the first manifestation of a disorder, and frequently are the reason for parents and patients to pursue medical evaluation. Prompt recognition and diagnosis of exanthems is desirable and may dictate that other examinations be performed to assess for systemic associations. The majority of childhood exanthems are caused by virus, and less often by bacterial or rickettsial agents. This article reviews an approach to a case of fever with rash emphasizing on the history and clinical examination.

Approach to a case of fever with rash

A febrile child with rash often presents a diagnostic challenge for physicians. The distinct morphological features and distribution of the rash along with a characteristic cluster of systemic features may give a clue to the clinician. A thorough history including onset, duration and type of fever, temporal association between fever and rash, sequence of distribution of rash, associated symptoms, presence of similar lesions in close contacts, recent intake of medicines, travel history, drug allergy and hygiene status of the household should be taken.

Careful physical examination entails close examination of the rash that includes morphology, configuration, distribution, progression, mode of subsidence and salient features of mucosal and systemic involvement. The common causes of fever with rash are given in Table 1. [1]

Table 1: Common causes of fever with rash

Infectious cases	**Viral infections**: Measles, rubella, erythema Infectiosum, roseola infantum, varicella, herpes simplex, infectious mononucleosis, coxsackie infections, dengue, chikungunya, papular acrodermatitis of childhood, asymmetrical periflexural exanthem, papular purpuric gloves and socks syndrome **Bacterial infections**: staphylococcal, streptococcus infections, meningococcemia **Rickettsial infections**
Non infectious causes	**Collagen vascular disorders**: Systemic lupus erythematosus, juvenile rheumatoid arthritis, Kawasaki disease, henoch-schonlein purpura, polyarteritis nodosa, wegners granulomatosis **Drug reactions:** Steven-Johnsons syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms

Clinical Features

Exanthems are classified based on morphology of the lesions into macular, maculopapular, diffuse erythema, vesicular, pustular, petechie, papular, nodular forms, and have been described also as morbilliform ('measles-like'), rubelliform ('rubella-like'), scarlatiniform ('scarlet fever-like'), or urticarial.

Measles (Rubeola)

Measles is an acute febrile illness caused by RNA virus of the genus morbillivirus in the paramyxoviridae family. It is characterized by a distinct prodromal phase with fever, coryza, brassy cough, and conjunctival congestion (3C's of measles). Koplik spots are pathognomic sign of measles consisting of gray white sand-like lesions with surrounding erythema in the buccal mucosa opposite the lower second molar tooth. [2] Erythematous, confluent, maculopapular rash develops usually on the fourth day of fever, beginning behind the ears and forehead and progressing downward spares palms and soles. The rash resolves in the same order with residual brownish discoloration and desquamation which fades over the

next 10 day.

Atypical measles is seen in children vaccinated with killed vaccine. Peripheral petechial eruption occurs on hands and feet which progress to vesicles, purpura. Modified measles occurs in previously vaccinated children and in this the prodrome and exanthem is milder and of shorter duration. Koplik spots may be absent.

Rubella

Rubella is seen in adolescent and adults and presents with fever , rash and cervical lymphadenopathy. The rash consists of minute, discrete macules, in contrast to the confluent rash of measles. The rash appears within 24 hours of onset prodromal symptoms, spreads rapidly in a cephalocaudal manner and begins to involute after 1-3 days in the same order. Posterior cervical and postauricular lymphadenopathy, although not pathognomonic, is commonly seen. Petechiae on soft palate (forschimer spots) can occur.

Erythema Infectiosum (fifth disease)

Erythema Infectiosum is caused by parvovirus B19. Has a mild prodromal symptoms and begins as a homogenous erythema over the cheeks (slapped cheek appearance-stage I) [figure 1] and progresses to a lacy reticulate macula urticarial exanthem over the proximal extremities and occasionally over distal extremities and trunk (stage II). The rash may wax and wane for 6 to 8 weeks triggered by local irritant, high temperature, and emotional stress (stage III). Slapped cheek appearance needs to be differentiated from lupus erythematosus, juvenile rheumatoid arthritis, erysipelas and drug reaction. [1,3]

Parvovirus also causes papular-purpuric gloves and socks syndrome (PPGS) which consists of oedema and erythema of both hands and feet, associated with petechiae and purpura.

Roseola Infantum

Children infected with roseola infantum (HHV6) exhibit a sudden high fever lasting for 3-5 days. With cessation of fever, discrete macular or maculopapular rash over neck and trunk which begins to disappear

in a few hours. These children have a 10% risk of febrile convulsions. Pityriasis rosea (PR), commonly affecting adolescents and young adults, has been associated with HHV6 and HHV7.

Infectious mononucleosis:

Exanthem is of 2 types. It can occur as macular, petechial, scarlintiform, urticarial or erythema multiforme like rash. It also follows administration of antibiotics (ampicillin), and the rash occurs 5-9 days after starting the antibiotic. [4]

Varicella

Rash of varicella occurs in crops, which evolves through the stages of macule, papule, vesicle, and crusts involving mainly the trunk and proximal end of extremities. Fever subsides 2-4 days after appearance of rash and the rash disappears after 3-7 days, leaving behind hypo- or hyperpigmented macules persisting for days to weeks. Breakthrough varicella occurs in vaccinated children where vesicles are fewer in number.

Hand foot mouth disease (HFMD)

HFMD is highly contagious caused by coxsackie and enterovirus. After a prodrome of 2-4 days, large (2-8 mm), oval, blisters with erythematous base develop over hands, elbow joint, upper limbs, buttocks [figure 2]. Painful aphthous ulcers are seen in the mouth. The rash resolves in 5-7 days. Onychomadesis and beau's line commonly occur post HFMD.

Gianotii crosti syndrome (GCS)

GCS also called papular acrodermatitis of childhood affects children between 1 and 6 years of age. Many viruses have been implicated to cause this disease, namely hepatitis B, EBV, cytomegalovirus, and coxsackie virus. The rash that follows a prodrome of fever and respiratory symptoms consists of monomorphic and symmetric,flat-topped pink-brown papules distributed classically on cheeks, extensor extremities, and buttocks. Hemorrhagic or eczematous papules may also be seen [figure3]. The rash lasts

for 6 to 8 weeks, sometimes longer. These rashes needs to be differentiated from papular urticaria, scabies, atopic dermatitis, lichen planus, erythema multiforme and P Rosea

Asymmetrical periflexural exanthem

Known as unilateral laterothoracic exanthem(ULE) is seen commonly between 1-5 years of age. Onset of skin eruption is unilateral and distributed unilaterally on trunk, often extends towards the axilla. Lesions spread centrifugally and they can be of various morphologies macules, papules, eczematous, morbilliform, annular or reticulate. Desquamation is common during the healing stage.

Dengue rash

Children with dengue fever present with sudden onset of high grade fever associated with facial flushing, headache, myalgia, arthralgia, and abdominal pain. Within 48 hours of onset of fever, a transient generalized macular rash develops. Fever may subside after 2-7 days, only to reappear after 1-2 days, demonstrating the typical biphasic pattern. Generalized maculopapular rash occurs all over the body sparing the palms and soles. Islands of sparing of skin in a background of ocean of erythema are a distinctive pattern seen during resolving phase. [5]

Chikungunya rash

Chikungunya rash presents as maculopapular, vesicles, bullae, pigmentation, desquamation, urticarial, purpuric, vasculitis and acrocyanosis. [6] Chikungunya pigmentation can occur at birth if mother is infected with chikungunya during pregnancy. Speckled hyperpigmentation is seen on face, trunk and extremities. Nasal pigmentation is a very striking feature of chikungunya rash [figure 4].

Petechial and purpuric rashes

Petechial and purpuric rashes are seen in meningococcal infection, henoch schonlein purpura, purpura fulminans, rickettsial infections, enteroviral infections and bacterial septicaemia. Meningococcemia is characterized mainly by fever with petechiae, but other transient lesions resembling a viral

maculopapular rash may also be seen. The petechiae are often raised with a "smudged" appearance involving trunk and extremities. Gangrenous hemorrhagic areas resembling purpura fulminans are seen in fulminant meningococcemia which is also associated with adrenal hemorrhage, hypotension, multiorgan failure (MOF) with or without meningitis.

Other infections

Staphylococcal scalded skin syndrome (SSSS) affects predominantly children below 5 years of age. SSSS presents as flaccid vesicles, bullae, in a background of scarlatiniform erythema, transforming into a wrinkled paper appearance with peeling of large sheets of epidermis. Healing occurs within 10-15 days without scarring. [7] Scarlet fever is characterized by a rash and strawberry tongue appearing 1-2 days after an upper respiratory tract infection. The rash is typically diffuse, erythematous, blanchable, and finely papular (like sandpaper) beginning around the neck spreading over trunk and extremities, sparing the face. Pastia lines are seen in flexural areas. The rash fades with desquamation after 3-4 days. Rickettsial fever usually have varying combination of features including fever, headache, myalgia, hepatosplenomegaly, and lymphadenopathy along with rash. The rash is macular or maculopapular, occasionally petechial. The diseases may be associated with a typical painless eschar with an erythematous rim at the site of vector bite. [8]

Non Infectious causes of fever with rash

Any child presenting with fever with rash, drug reaction must be ruled out. Through history of drug intake and possible association with rash must be examined. Drug reactions can present as maculopapular rash, urticarial, SJS, TEN and drug hypersensitivity syndrome [figure 5]. [9]The difference between drug reaction and viral exanthem is shown in Table 2. Kawasaki disease is a diagnosis of exclusion. It presents as high grade fever, conjunctivitis, lip fissuring, cervical lymphadenopathy, polymorphous non vesicular rash, edema of hands and feet and resolves with characteristic periungual and perianal desquamation. Risk of coronary aneurysms is high in the first week of the disease. [10] Other non infectious causes of fever with rash include collagen vascular disorder and Vasculitis.

Table 2: Differences between viral exanthem and drug reactions

Viral Exanthem	Drug Reaction
Constitutional symptoms are present	Constitutional symptoms are less
Onset of lesions starts from face, progresses to trunk and extremities and resolves in same pattern	Abrupt onset of skin lesions
Pruritus absent	Pruritus present
Maculopapular rash Palms and soles may/not involved	Dusky erythema Palms and soles involved
Systemic involvement is less involved	Systemic involvement more common
Investigations – Lymphopenia, neutropenia	Eosinophilia present

Conclusion

Evaluating a febrile child with rash is challenging as the differential diagnosis is extensive. Organized approach is necessary. Many of the exanthems are self limiting. Prompt detection of early signs of life threatening skin eruptions is essential to prevent mortality.

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Fig 1: Slapped cheek appearance in erythema infectiosum

Fig 2: Multiple papulovesicles on the palms in hand-foot-mouth disease

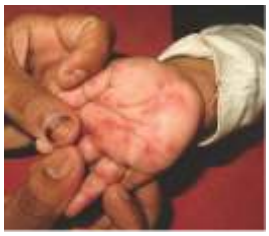


Fig 3: Multiple monomorphic erythematous papules present bilaterally symmetrically on the lower limbs

Fig 4: Striking nasal pigmentation seen in chikungunya fever

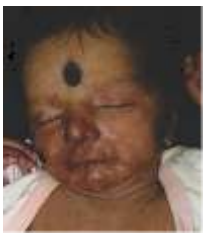
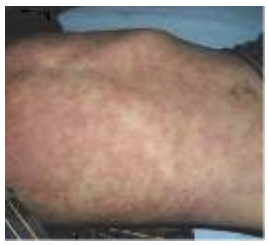


Fig 5: Diffuse maculopapular rash seen in drug hypersensitivity syndrome



Antimalarial drugs in Dermatology

Dr. Eshwari L Assistant Professor BMCRI Bangalore

History

Though primarily synthesized to treat malaria, antimalarials have now been extensively accepted and approved to treat cutaneous lupus. Payne is credited with being the first in 1894 to prescribe an antimalarial, quinine, to treat patients with lupus. Quinine is derived from the natural bark of the South American cinchona tree, which grows on the slopes of the Andes mountains. During World War II, when the world lost its natural supply of quinine, efforts to synthesize synthetic analogs began. In 1943, there emerged the infamous yellow staining 'American atabrine' (quinacrine, mepacrine). The ongoing search for safer synthetic antimalarials led to the discovery of chloroquine phosphate and hydroxychloroquine sulfate.

Chemistry and mechanism of action

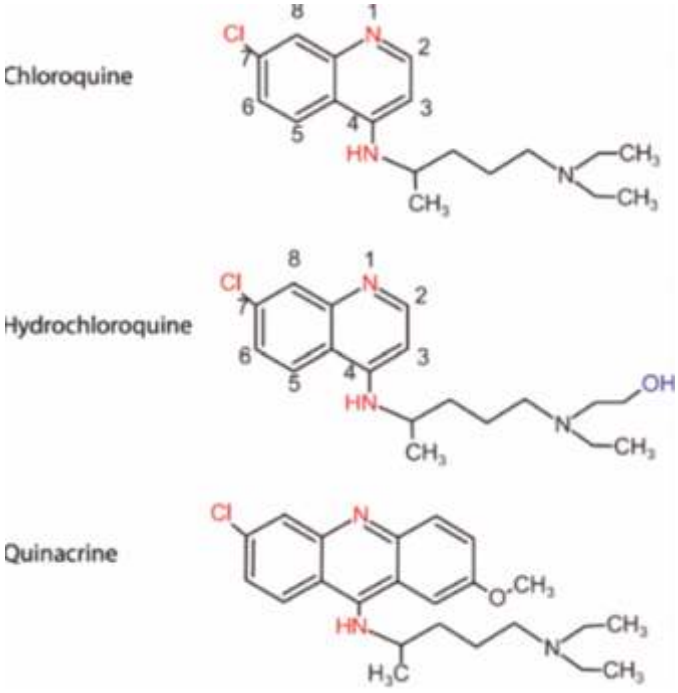


Figure 1: Structure of the 4-aminoquinoline chloroquine and hydroxychloroquine as well as the acridine dye quinacrine.

Chloroquine (7-chloro-4-[4'-diethylamino-1'-methyl-butylamino]-quinoline (CQ) in its pure form, is a white, crystalline, bitter-tasting powder. Hydroxychloroquine(HCQ) is a derivative of chloroquine . The two substances do not differ with regard to their mechanism of action, pharmacokinetics, toxicology, side effects, and indications.

CQ/HCQ have immunomodulatory, anti-inflammatory, and antiproliferative properties; they

alleviate UV-induced inflammation, inhibit thrombocyte aggregation, enhance glucose tolerance, and cause increased porphyrin excretion. These are the effects that makes these substances useful for therapy. **The major proposed mechanism of action of antimalarial drugs is interference with lysosomal acidification. Consequences of this lysosomotropic effect within macrophages, dendritic cells and lymphocytes are felt to underlay the therapeutic anti inflammatory effect of these drugs.**

Mechanism of action[2]

Immunomodulatory	Diminished class II antigen presentation Diminished response to mitogenic stimuli
Anti-inflammatory	Diminished arachidonic acid release and prostaglandin synthesis; reduced bradykinin effect Diminished leukotriene synthesis and histamine release Diminished antigen presentation and immune stimulation
Antiproliferative	Inhibition of DNA/RNA biosynthesis and polymerase
UV absorption	Increased UV filtration as a consequence of accumulation in melanin and increased epidermal concentrations Inhibition of UV-induced inflammatory reactions
Coagulation	Inhibition of thrombocyte aggregation
Metabolic	Reduced cholesterol, triglyceride, LDL levels Increased excretion of porphyrins

Quinacrine is a yellow acridine dye. It is no longer commercially available.

Pharmacodynamics

CQ/HCQ are taken orally and are almost completely absorbed. The concentration of CQ/HCQ in the skin is 100–200 times higher than in plasma. There is virtually no accumulation of CQ/HCQ in adipose tissue. CQ/HCQ accumulate in "deep compartments" (distribution volumes > 100 l/kg) and especially in melanin. The half-life of CQ/HCQ can be as long as 50 days. In some patients, more than 50 % of CQ/HCQ is eliminated by the kidneys. Plasma levels of CQ/HCQ primarily depend on reverse diffusion from the deep compartments. Higher plasma levels have been shown to be related to an increased risk of side effects.

Dosing

To avoid adverse effects, the maximum dosage should be adjusted according to the ideal body weight of the patient. For chloroquine this is 3.5(–4) mg/kg of ideal body weight and hydroxychloroquine at 6(–6.5) mg/kg of ideal body weight.

Formulas for calculating this idealweight are as follows:

for women (height in cm - 100) - 15%and for men (height in cm - 100) - 10%. If the patient weighs less than the ideal weight, the doses are adjusted according to the real weight. Dose calculation using these formulas is particularly important for long-term treatment and in small patients, in whom there is a risk of overdose with the standard antimalarial doses. Dosage must be further decreased in patients with impaired kidney or liver function. The standard dosage of quinacrine is 100 mg/daily.

Adverse effects of chloroquine/hydroxychloroquine[2]

ORGAN	SYMPTOMS
Nonspecific	Nausea, abdominal cramps, bloating, diarrhea, acid reflux, difficulty concentrating, sleep disorders
Eyes	Irreversible retinopathy Corneal deposits Accommodation disorders
Hair	Whitening, hair loss
CNS	Sleep disorders, confusion, dizziness, headache, paresthesia/dysesthesia drowsiness, fatigue, anxiety Psychoses, epileptic seizures
Ears	Hearing loss, tinnitus
Skin	Hyperpigmentation Exanthems, exfoliative reactions Phototoxic/allergic reactions Pruritus Hyperpigmentation- Gray discoloration on shins, palate, subungual; reversible
Locomotor system	Myopathies/neuromyopathies
Cardiovascular system	Depression of T wave; possible chronic toxicity in conduction disorders Drop in blood pressure Cardiomyopathy
Liver/gallbladder	Elevated transaminase
Kidney	Phospholipidosis
Blood/lymphatic system	Pancytopenia, agranulocytosis, thrombocytopenia Eosinophilic methemoglobinemia
Metabolism	Exacerbation of porphyria

CQ/HCQ must be kept out of reach of small children. Even ingestion of only a few tablets can lead to fatality. Intoxication, which can cause cardiac arrest, is difficult to counteract HCQ reportedly has fewer side effects than CQ, but is also less effective. CQ/HCQ deposits in the cornea are not critical. CQ/HCQ can, very rarely, cause various types of rashes. Quinacrine can cause yellowish discoloration of the skin. Antimalarial drugs can exacerbate psoriasis. Conduction disorders are possible, but rare at therapeutic dosages. The hemolytic effects associated with CQ/HCQ are minimal. The benefits and risks of taking antimalarial drugs during pregnancy should be considered individually. In pregnant women being treated for lupus, the use of HCQ is considered safe.

Contraindications

- Patients with retinopathy.
- Patients with hypersensitivity reactions to HCQ or CQ.
- Concomitant bone marrow suppressive therapy

Other Absolute contraindications:

- Diseases of the hematopoietic system
- Pregnancy and nursing
- combination with hepatotoxic agents
- combination with monoamine oxidase (MAO) inhibitors.
- Use is also limited in patients with severe liver or kidney dysfunction or psoriasis.

Relative contraindications

- Neuromuscular disorders such as myasthenia gravis or psychoses.
- Pre-existing porphyria cutanea tarda,
- Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency

Laboratory monitoring

Ophthalmological examinations (fundoscopy, vision field testing, color vision testing, Amsler grid test) are recommended before starting therapy or within the first few months of treatment especially for patients over 65 or with renal or liver insufficiency.

Several studies have found that there are no relevant hematological or hepatotoxic effects of antimalarial drugs if the maximum daily dosage is not exceeded. American College of Rheumatology has explicitly stated that no laboratory studies are needed before or during therapy. It is advisable, however, to get baseline results for a blood differential and liver values before starting antimalarial therapy in order to rule out any pre-existing pathological changes. For patients taking quinacrine, the blood differential (very rare: aplastic anemia) should be assessed at the start of therapy, and afterward every 3 to 4 months, and later every 6 months.

Confirmed indications

1. **Lupus erythematosus-** LE is the only dermatologic indication approved by the US Food and Drug Administration
1. Cutaneous lupus erythematosus
2. Chronic cutaneous lupus erythematosus (DLE)- It can take up to 8 weeks before the maximum effectiveness of CQ/HCQ is reached. The combination of CQ or HCQ with quinacrine acts synergistically.
2. Lupus panniculitis
3. Subacute cutaneous lupus erythematosus (SCLE)
4. Lupus erythematosus tumidus
5. Acute cutaneous LE/systemic lupus erythematosus (ACLE/SLE)

In patients with systemic lupus, CQ/HCQ prevent exacerbations and prolong survival.

2. REM syndrome
3. Porphyria cutanea tarda (PCT)

   For PCT, CQ/HCQ are given in much lower dosages than usual: twice weekly 2* 125 mg CQ or 2* 100 mg HCQ.
4. Chronic ulcerative stomatitis

   Suitable indications

1. Sarcoidosis

Indications for administering CQ or HCQ in patients with sarcoidosis are: chronic disfiguring skin lesions, progressive extracutaneous lesions in patients in whom steroid therapy is contraindicated, adjuvant therapy with steroid treatment, continued neuro-sarcoidosis with steroid failure. Hypercalcemia in sarcoidosis, but not in B-cell lymphoma, has shown improvement after hydroxychloroquine therapy.

2. Dermatomyositis

Individual therapy attempts

In the following indications, treatment may be attempted if standard therapies fail.

- Sjögren syndrome
- Polymorphous light eruption
- Atopic dermatitis
- Eosinophilic fasciitis
- Hereditary bullous epidermolysis
- Granuloma anulare
- Lichen planus mucosae
- Lichen sclerosus et atrophicus
- Morphea
- Necrobiosis lipoidica
- Panniculitis (chronic erythema nodosum, lipoatrophic panniculitis)
- Solar urticarial
- Urticarial vasculitis

Non-dermatological indications

- Thrombosis prophylaxis
- Antiphospholipid syndrome

CQ/HCQ should be considered the primary preventive measure against thromboembolism in patients

with SLE or phospholipid antibodies.

Effects on blood lipids -CQ/HCQ diminish the effects of corticosteroids on blood lipids and glucose.

Conclusions for practicing dermatologists:

When compared with other immunomodulatory agents, antimalarials have a favorable safety profile. Risk may be minimized by observing the following principles. The incidence of side effects depends heavily on plasma levels of the drug. These in turn are a result of reverse diffusion of CQ/HCQ from the "deep compartments." Antimalarial drugs are not stored in adipose tissue. Thus, the key to avoiding retinopathy is to observe the maximum recommended daily dosages of 3.5(–4) mg/kg chloroquine (ideal body weight) and 6(–6.5) mg/kg hydroxychloroquine. If there is delayed elimination due to renal or liver dysfunction, the dosage should be further reduced. Ophthalmological monitoring during the first few months of therapy are advised, and later in larger intervals. If the above-mentioned guidelines are followed, CQ/HCQ may even be given over longer periods of time with minimal risk.

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Gianotti-Crosti Syndrome: Common but underdiagnosed condition

Introduction

Gianotti-Crosti syndrome (GCS) is commonly seen in our practice but sometimes may be missed. It is a misnomer as it is not a symptom complex. GCS is a self limiting viral exanthem of childhood characterized by multiple, monomorphic, pruritic papules or papulovesicles distributed symmetrically on the acral regions. It is also known as papular acrodermatitis of childhood, infantile papular acrodermatitis, papulovesicular acrolocated syndrome or Crosti-Gianotii disease. [1] It is rarely seen in adults.

History

GCS was first described by Gianotti in 1955, when he noticed a unique rash localized only to face and extremities in three children. [2, 3] He also named it as papular acrodermatitis of childhood. Since then many new features like increased liver enzymes, presence of virus particles in liver were observed along with GCS in 1960. In 1970, the role of hepatitis B infection in GCS was confirmed by Gianotti. [4] Further studies showed that not all cases of GCS are associated with hepatitis B virus infection.

Epidemiology

GCS is seen worldwide, but most of the epidemiological studies have been reported from Japan and Italy. In these studies majority of the cases was seen in infants and young children and were related to Hepatitis B and Epstein Barr virus infection (EBV). [5] No seasonal variation has been reported in literature for GCS. It is seen more in children between the age group of 6 months to 14 years. There is no race or sex predisposition. The eruption is seen more in spring and early summer.

Etiology

GCS is a cutaneous hypersensitivity response to viral infection. EBV and Hepatitis B virus (ayw/ adr subtypes) infection is the most common etiological agent of GCS. EBV appears to be the most common causative agent worldwide. Other viruses associated with GCS include hepatitis A, hepatitis C,

herpesvirus 6, cytomegalovirus, coxsackievirus, adenovirus, enterovirus, echovirus, parvovirus B19, poxvirus, rotavirus, rubella, respiratory syncitial virus, polio virus, parainfluenza, molluscum contagiosum virus and HIV infection. [6] Other rare causes other than virus include Bartonella henselae, Mycoplasma pneumonia and milkers nodules. [7, 8] In a study published in India, hepatitis B infection was not associated with GCS. [9] Many cases following vaccination has been reported which includes diphtheria, pertussis and tetanus (DPT), vaccinia, influenza, polio, measles, MMR, hepatitis A and B, BCG, haemophilus influenza b, and Japanese encephalitis vaccination. [10] There is a history of atopic back ground in many children with GCS.

Pathogenesis

The exact underlying pathophysiological mechanisms are not clear in GCS. Various hypotheses include immunological alteration, delayed hypersensitivity reaction to various triggers or immune complex deposition. However immunohistochemistry and electron microscopy findings have not demonstrated the presence of viral particles or antigens in skin lesion, suggesting that rash of GCS is not due to direct interaction between viral antigens and immune cells in the skin. It is due to stimulation of immune system following viral infection. [11]

Clinical Features

GCS is characterized by monomorphic, flat topped papules, erythematous papules or papulovesicles, distributed symmetrically on the extensor aspect of upper and lower limbs, buttocks and face [figure 1]. Lesions may coalesce to form large plaques on elbows and knees. Trunk and flexural areas are relatively spared. Palms and soles are rarely involved. Mucous membrane may not be involved. Pruritus may be mild to moderate. Koebner phenomenon is present during the early and acute stage. The rash usually begins on the thighs and buttocks and slowly progress to involve extensor aspect of arms and face. [6, 12] Hemmorhagic lesions is also reported in literature. [13] Constitutional symptoms may be mild to moderate. GCS may be preceded by upper respiratory tract infection, pharyngitis, tonsillitis, diarrhea, fever, malaise, nausea and vomiting. Lymphadenopathy is seen in one-third of patients. Cervical, axillary

or inguinal lymphnodes may be involved. Recurrences are rarely seen. If GCS is associated with hepatitis B infection hepatomegaly is seen. Chronic active hepatitis is extremely rare. Hepatic involvement is present at the onset of rash or may appear 1- 2 weeks after the rash appears. [14] Lesions resolve by 6- 8 weeks by desquamation. Rarely lesions may persist beyond 8 weeks.

Diagnostic Criteria

Diagnostic criteria for GCS have been proposed by Chuh et al in 2001 [Table 1]. [1]

Table 1: Diagnostic criteria for GCS

Positive clinical features	Negative clinical features
• Monomorphous, flat topped, pink-brown papules or papulovesicles 1-10mm in diameter • Symmetry • Any three or all four sites involved: cheeks, buttocks, extensor surfaces of forearm, extensor surfaces of legs • Duration of a tleast 10 days	• Extensive truncal lesions • Scaly lesions

Diagnosis of GCS is considered if on at least one occasion or clinical encounter exhibits all positive clinical features or on all occasions does not exhibit negative clinical features or none of the differential diagnosis is considered to be more likely than GCS or if lesional biopsy is performed, the findings are consistent with GCS.

Differential Diagnosis

Differential diagnosis of GCS is listed in Table 2.

Common differential diagnosis	Uncommon differential diagnosis
• Papular urticaria • Scabies • Lichen planus • Erythema multiforme • Atopic dermatitis • Hand-foot-mouth disease • Asymmetrical periflexural exanthem	• Pityriasis Rosea • Infectious mononucleosis • Frictional lichenoid dermatitis • PLEVA • H S Purpura • Langerhans cell histiocytosis

Diagnosis of GCS is mainly clinical. The characteristic morphology and distribution is distinctive. Papular urticaria is one of the most common disorder that must be differentiated from GCS in children. Papular urticaria occurs on exposed sites as excoriated papules or erythematous edematous papules with central vesicle. Diagnosing GCS in adults is difficult as it is rarely seen.

Investigations

Leucopenia or slight leucocytosis, increased monocytes, is seen. Erythrocyte sedimentation rate is normal. Abnormal liver enzymes may be present in EBV or CMV infection. Increased liver enzymes like glutamicoxaloacetic transminase and gluatmic-pyruvic transaminase titre (1000-2000 U/ml) is associated with hepatitis B infection. Skin biopsy may be necessary to exclude other differential diagnosis. Histopathology features include moderate to dense lymphocytic infiltrate along with histiocytes in the perivascular area and endothelial swelling. [6]

Treatment

There is no specific treatment. As the disease is self limiting, only symptomatic treatment is necessary. Emollients, mild to mid potent topical steroid and oral antihistamines can be used which provides minimal relief. Systemic corticosteroid pulse therapy is given for severe cases. Hepatitis B associated GCS should be monitored and treated appropriately. [15]

Prognosis

Prognosis is good as the condition is self limiting within 3-8 weeks. Complications are rare. Rash resolves with no scarring. Parents must be counseled about the nature and course of the disorder.

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Figure 1: Multiple monomorphic erythematous papules with koebner phenomenon present bilaterally symmetrical on extensor aspect of lower legs.

Pruritus in the elderly: Diagnostic and therapeutic approach

Dr. Prabhakar M Sangolli, Consultant Dermatologist, Bangalore, Karnataka India

Pruritus is an unpleasant sensation inducing the desire to scratch. Where acute itch may last up to 6 months, chronic itch persists beyond 6 months. Itch severely affects QOL equivalent to QOL of a patient with chronic pain.

Elderly patients with chronic pruritus account for nearly 20 % of hospital admissions.

Pathophysiology: Að and type C fibres are involved. Mediators include histamine, prostaglandin derivatives, neuropeptides, bradykinin, enzymes etc .. Thalamus and parietal cortex are the higher centres

Classification

Dermatological causes: Common causes include xerosi s, photosensitivity, atopic dermatitis, dermatophyte infection , candidiasis ,herpes zoster, perianal infection with fecal and other bacterial infections etc..

Neurological causes: Small fiber neuropathy (SFN) is one of the common neurological cause of senile itch. Othere causes include multiple sclerosis (MS), cerebral tumors,stroke etc

Psychological causes: Depressed and anxious patients ,often present severe itch. Except excoriations, they may not have obvious dermatological conditions.

Systemic causes: Obstructive hepatic disorders, chronic renal failure, Hodgkin's lymphoma,polycythemia vera are some of the conditions which need to be looked into

Drugs : Common drugs implicated include anti hypertensives (ARBs ,ACEI,),drugs causing liver and renal damage, opioids,drugs inducing urticaria and angioedema, SJS/TEN etc..

Evaluation and management

History taking: Localized and generalized itch can have different etiologies. Nocturnal itching is characteristically described in scabies and SFN. Certain activities like applying cold water may relieve itching. Systemic diseases like DM, thyroid disorders, hepatic and renal diseases, neoplasms need to be ruled out. History of previous surgeries may give clue to underlying pathology. Drug allergy and cross sensitivity also needs to be ruled out. Family history of DM, thyroid disorders, liver diseases have to be investigated.

Cutaneous examination: Presence of pallor, icterus, hemorrhage, increased temperature of the lesions may give clue underlying pathology. Dermatographism needs to be tested to rule out factitious urticaria

Investigations: CBC with variations in cell count may point towards infectious,allergic or malignant etiology. Advanced investigations like LFT, RFT, diabetic and thyroid profile,sonological,radiological and imaging techniques may be employed to arrive at etiological diagnosis

Treatment

General measures include soothening bath using superfatted soap or syndet bar/soap substitutes followed by application of moisturizers which will be of great help in alleviating pruritus. Patients need to be told to desist from scratching and finger nails need to be kept trimmed

Topical therapy :

Topical steroid: Relieve itch in AD and psoriasis. Topical calcineurin inhibitors are effective in AD and pruruigo nodularis,. Topical anesthetic pramoxine is useful in uremic pruruitus. Topical polidocanol is helpful in xerosis,AD and psoriasis.Capsaicin has been employed in neuropathic,dermatological and systemic itch with varied results. Preparation containing camphor,menthol and phenol is a popular anti pruritic lotion. Topical antihistamine 5 % doxepin has been tried in LSC, nummular eczema and AD. Topical cannabinoids are found to act on CB_2 receptors to offer relief in patients with AD,LSC,prurigo nodularis and CKD.Topical aspirin/dichlormethane combination is an effective steroid sparing anti pruritic combination

Systemic therapy:

Anti histamines : Urticaria /angioedema

Mirtazapine (5-HT_2/$_3$ antagonist): Hepatic,renal and cancer induced itch

Ondansetron (5 HT_2 antagonist): Cholestatic pruritus

Opioid antagonist: Naltrexone - Hepatic, renal pruritus , urticaria, AD, prurigo nodularis (PN),opioid induced pruritus. Opioid agonist (Butorphanol) is useful in intractable itching

Neuroleptics: Gabapentin: Neuropathic pruritus

Other: NBUVB: Uremic pruritus

Psychotherapy: Habit reversal therapy, CBT, aromatherapy etc.. are useful in AD

Acupuncture: Neuropathic pruritus, uremic pruritus and PN

Treatment of pruritus due to systemic disease:

Cholestatic pruritus: Cholestyramine and colestipol are quite effective Uremic pruritus: Topical tacrolimus, 1 % pramoxine lotion and oral gabapentin are effective Hematological malignancies: Iron supplements are useful in patients with iron deficiency anemia. Treatment of underlying malignancy may relieve pruritus. Diagnosis and treatment of pruritus in the elderly needs detailed history, taking thorough physical examination and appropriate therapy based on overall assessment of general health of the patient.

Abbreviations: PN:Prurigo nodularis ,AD:Atopic dermatitis,LSC:Lichen simplex chronicus, CBT:Cognitive and behavioural therapy, CKD :Chronic kidney disease, SFN: Small fiber neuropathy, ARB:angiotensin receptor blocker

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Urticaria : Current insights

Prabhakar M Sangolli, MD,DVD,DNB
Consultant Dermatologist, Bengaluru

Urticaria is a common disorder with complex etiology. It severely affects QOL of the patient, Urticaria poses great diagnostic and therapeutic challenge.

Urticarial is arbitrarily classified as acute and chronic spontaneous urticaria, inducible urticaria and other inducible urticarias Acute spontaneous urticaria usually lasts for about 3 weeks and in nearly 60 % of cases cause can be identified. These include viral and bacterial infections,drugs and rarely food Nearly 50% of patients with chronic spontaneous urticarial (CSU) have detectable antibodies against high affinity IgE receptors. NSAIDs, emotional stress, foci of infections,thyroid disorders are usually detected. And nearly 50 %of patients have co existing angioedema which is a bad prognostic factor Dermatographism,delayed pressure urticaria,cholinergic urticaria,cold urticaria are all encountered in daily practice. Inducible urticaria also co-exist with chronic spontaneous urticaria.

Dermographism can last up to 7 years. Delayed pressure urticarial is more common in men and can persist as long as 10 years. Acquired cold urticaria is divided into 9 types, idiopathic being the commonest. Infections,neoplasia,auto immune diseases can co-exist with cold urticaria.Solar urticaria can be due to sun light of wavelength between 280 to 760nm.Cholinergic urticarial lesions appear when there is a rise in core body temperature due to hot bath, exercise, emotional stress etc.. Aquagenic urticaria is common among young women. Auto reactivity, autoimmunity, type 1 hypersensitivity, drugs like NSAIDS, infections, systemic diseases like autoimmune thyroid disorders, mental stress can all aggravate chronic spontaneous urticaria Cutaneous and systemic urticarial syndromes pose diagnostic challenge.

Lab investigations may not be necessary in patients with acute urticaria, except in patients where type 1 hypersensitivity is suspected. Co morbid conditions, physical urticaria need to be excluded in patients with CSU. ASST is helpful to rule out chronic auto immune urticaria. Urticaria activity score (UAS-7) is assessed to quantify the severity. CBC,ESR,and CRP may be carried out in patients with chronic spontaneous urticaria to rule out inflammatory process as in urticarial vasculitis. Thyroid function tests are carried out to rule out auto immune thyroiditis.

Treatment involves identifying and eliminating the cause, avoiding and elimination of eliciting stimulus and judicious use of antihistamines (H_1 inverse agonists) and anti-inflammatory and immunosuppressive drugs. Second generation histamines in standard dose, followed by 4 fold up dosing of 2^{nd} generation anti histamine and sometimes steroid rescue therapy for 1-2 weeks and finally omalizumab administration are the three essential steps employed in the management of severe, relapsing CSU.

Urticaria poses huge diagnostic and therapeutic challenge to the treating clinician

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