Gianotti-Crosti syndrome, pityriasis rosea, asymmetrical periflexural exanthem, unilateral mediothoracic exanthem, eruptive pseudoangiomatosis, and papular-purpuric gloves and socks syndrome: a brief review and arguments for diagnostic criteria

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Abstract

Several exanthems including *Gianotti-Crosti syndrome*, pityriasis rosea, asymmetrical periflexural exanthem, eruptive pseudoangiomatosis, and papular-purpuric gloves and socks syndrome are suspected to be caused by viruses. These viruses are potentially dangerous. *Gianotti-Crosti syndrome* is related to hepatitis B virus infection which is the commonest cause of hepatocellular carcinoma, and Epstein-Barr virus infection which is related to nasopharyngeal carcinoma. Pityriasis rosea has been suspected to be related to human herpesvirus 7 and 8 infections, with the significance of the former still largely unknown, and the latter being a known cause of Kaposi's sarcoma. Papular-purpuric gloves and socks syndrome is significantly associated with human B19 erythrovirus infection which can lead to aplastic anemia in individuals with congenital hemoglobinopathies, and when transmitted to pregnant women, can cause spontaneous abortions and congenital anomalies. With viral DNA sequence detection technologies, false positive results are common. We can no longer apply Koch's postulates to establish cause-effect relationships. Biological properties of some viruses including lifelong latent infection, asymptomatic shedding, and endogenous reactivation render virological results on various body tissues difficult to interpret. We might not be able to confirm or refute viral causes for these rashes in the near future. Owing to the relatively small number of patients, virological and epidemiology studies, and treatment trials usually recruit few study and control subjects. This leads to low statistical powers and thus results have little clinical significance. Moreover, studies with few patients are less likely to be accepted by mainstream dermatology journals, leading to publication bias. Aggregation of data by meta-analyses on many studies each with a small number of patients can theoretically elevate the power of the results. Techniques are also in place to compensate for publication bias. However, these are not currently feasible owing to different inclusion and exclusion criteria in clinical studies and treatment trials. The diagnoses of these rashes are based on clinical assessment. Investigations only serve to exclude important differential diagnoses. A wide spectrum of clinical features is seen, and clinical features can vary across different populations. The terminologies used to define these rashes are confusing, and even more so are the atypical forms and variants. Previously reported virological and epidemiological results for these rashes are conflicting in many aspects. The cause of such incongruence is unknown, but low homogeneity during diagnosis and subject recruitment might be one of the factors leading to these incongruent results. The establishment and proper validation of diagnostic criteria will facilitate clinical diagnosis, hasten recruitment into clinical studies, and allow results of different studies to be directly compared with each another. Meta-analyses and systematic reviews would be more valid. Diagnostic criteria also streamline clinical audits and surveillance of these diseases from community perspectives. However, over-dependence on diagnostic criteria in the face of conflicting clinical features is a potential pitfall. Clinical acumen and the experience of the clinicians cannot be replaced by diagnostic criteria. Diagnostic criteria should be validated and re-validated in response to the ever-changing manifestations of these intriguing rashes. We advocate the establishment and validation of diagnostic criteria of these rashes. We also encourage the ongoing conduction of studies with a small number of patients. However, for a wider purpose, these studies should recruit homogenous patient groups with a view towards future data aggregation.

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Introduction

The apparently programmed clinical courses, spontaneous remissions after 2-12 weeks, apparent immunities after the first eruptions, laboratory findings, and epidemiology findings led us to suspect that several skin eruptions, namely *Gianotti-Crosti syndrome* (GCS, also known as papular acrodermatitis of childhood)[1-3] (Figure 1), pityriasis rosea (PR)[4-6] (Figure 2 and Figure 3), asymmetrical periflexural exanthem (APE, also known as unilateral latero-thoracic exanthem)[7-9] (Figure 4), unilateral mediothoracic exanthem (UME, a variant of APE),[10] eruptive pseudoangiomatosis (EP),[11-13] and papular-purpuric gloves and socks syndrome (PPGSS),[14-16] are related to viral infections[17] (Figures 5-7).

Epidemiological evidence suggests that these exanthems could be much commoner than generally thought.[18-29] Most patients consult primary care clinicians in the first instance 30 who may significantly under-diagnose these rashes.[31]

The gravity of these exanthems is largely unknown. Severe complications might not have been noticed up to now, just as it took many years after the first case of Kawasaki disease was seen for coronary pathologies to be recognised as complications of this disease.[32] These exanthems can also cause significant morbidities and impacts on quality of life of patients.[33-35] With the viral etiologies unknown, antiviral therapies and immuno-modulating therapies are already in use.[36-38] These agents might cause significant adverse effects, and we have to gather adequate data to support or refute their use.

In this article, we shall briefly review our current understanding of these rashes, address the strengths and weaknesses of our present directions in investigations, explore whether the use of diagnostic criteria (DC) can overcome these weaknesses, and speculate on the potential pitfalls of utilizing such DC.

Virological investigations

GCS had been found to be significantly associated with hepatitis B virus (HBV) infection.[39-41] More recent research, however, implicates Epstein-Barr virus (EBV)[42-44] and other viruses[45,46] as alternative etiologies of GCS. HBV is the most common cause of hepatocellular carcinoma,[47] while EBV is significantly associated with Hodgkin's lymphoma, Burkitt's lymphoma, and nasopharyngeal carcinoma.[48]

Various viruses might cause APE, with no single virus being put under the spotlight.[26,49-51] No single virus has been significantly associated with EP.[52-54] PPGSS is significantly associated with human B19 erythrovirus (HB19EV, previously called parvovirus B19) infections.[55-57] However, other viruses are also implicated.[58-61] HB19EV infection can cause aplastic anemia,[62] the risk of which significantly increased if the patient had one of the congenital hemoglobinopathies.[62] If pregnant women get infected by HB19EV, the risks of spontaneous abortion and congenital anomalies rise sharply.[63]

Human herpesvirus (HHV)-7 infection has been suspected to be the cause of PR.[64-71] However, individual investigators reported controversial results.[72-75] Conflicting results were also reported for HHV-6a, 6b, and 8.[73,76,77] Cytomegalovirus,[75,78] EBV,[75,78] HB19EV,[77] *Chlamydia spp.*,[79] *Legionella spp.*,[79] and *Mycoplasma spp.*[79] infections have been suspected to be related to PR. HHV-8 causes Kaposi's sarcoma in patients with HIV infection. The long-term implications of HHV-6, -7, and -8 are still unknown.

Another debate concerns how many data are adequate to prove a causal relationship. The time-honoured Koch's postulates[80] seem to cater more for bacteria than for viruses. Hill's criteria for causality[81] might be more applicable to environmental non-infectious causes. Newer guidelines based on DNA sequence detection techniques[82] were not universally accepted. False positive results are particularly difficult to be minimized, as one viral DNA copy can theoretically lead to a positive result. The interpretation of DNA or messenger RNA transcripts sequence-based detection methods is particularly difficult for viruses with inherent pathogenetic properties of lifelong infection, latent infection, asymptomatic virus shedding, and endogenous reactivation. Apart from seroconversion signifying primary infection, IgM results are not convincing owing to cross-reactivity, while sequential IgG titers were of limited value unless investigations are conducted in parallel. Integrated approaches are now being advocated.[83-85] However, all studies mentioned above adopted different inclusion criteria, also making application of integrated approaches difficult.

We know, therefore, that although these rashes are usually self-limiting, they may be associated with viruses causing long-term complications. These associations may not be resolved in the near future.

Epidemiology studies

Descriptive epidemiology

There have been many epidemiological reports for GCS,[18-21,40] PR,[22-25] APE[26] and EP.[27-29] For GCS, five epidemics have been reported, three[20,21,41] being in Japan, affecting 54,[41] 153,[21] and 14[20] infants and young children, respectively. Most cases were related to HBV infection.[20,21,41] In an epidemic reported in Italy, 5 infants and young children were affected,[18] all found to have had recent EBV infection.[18] A mini-epidemic involving 3 children was also reported in India.[86]

Many systematic epidemiology studies[22-25,87-96] were reported for PR. A meta-analysis 97 reported that the overall incidence of PR was around 0.68 per 100 dermatological patients in specialist settings. In the community, the incidence was estimated to be 172.2 per 100,000 person-years,[89] with the prevalence being 0.6% at any one time for adolescents and young adults.[25] The male to female ratio is 1:1.44.[97]

Only one epidemiology report was available for APE,[26] concerning 67 infants and children over a period of 32 months. The male to female ratio was 1:1.23. For EP, three case series[52-54] were reported with 7 infants,[54] 9 adults,[52] and 7 adults,[53] the male to female ratio being 1:0.40,[54] 1:8.00,[52] and 1:6.00,[53] respectively. For PPGSS, there was a case series reporting 36 children at a median age of 23 months.[61]

We believe, therefore, that in the community these rashes may be more common than is usually thought. We may miss epidemics and mini-epidemics simply because many patients are not correctly diagnosed.

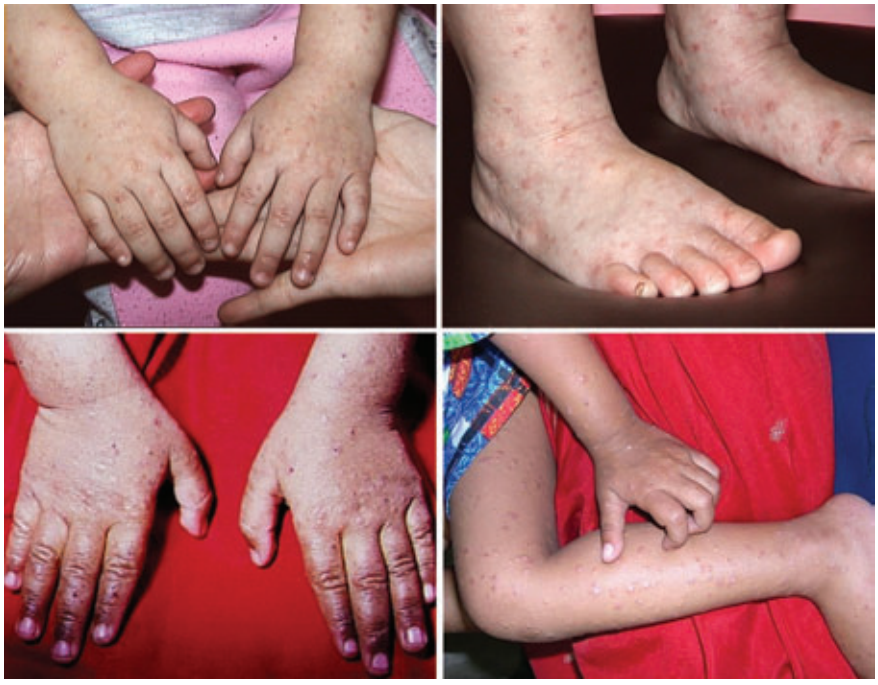

Figure 1. Papulovesicular lesions over the forearms, wrists, hands, legs, ankles, and feet of a Chinese child with Gianotti-Crosti syndrome (papular acrodermatitis of childhood).

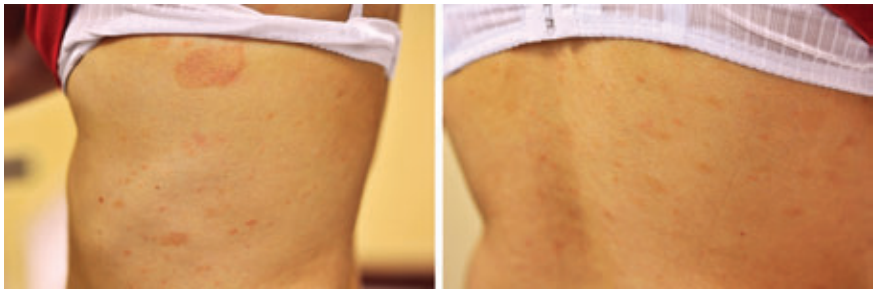

Figure 2. Typical lesions of pityriasis rosea on the trunk of a woman with pityriasis rosea.

Analytical epidemiology

Seasonal variations and geographical differences are the most commonly used analytical approaches, with other independent variables being contact history, immunization history, previous exanthems, previous febrile illnesses, and prodromal symptoms.[98] No analytical epidemiology study was reported for GCS. For PR, studies[87-94,96,99,100] reported conflicting results on seasonal variation. PR was reported not to be associated with climate data including the monthly mean temperature, mean total rainfall, and mean relative humidity.[100] No study was reported for APE, EP and PPGSS on these analytical variables.

Another analytic approach is temporal and spatial-temporal clustering. Clustering might substantiate diseases being contagious, and have been applied in Kawasaki disease.[101] Powerful analytical tools are now available to detect clustering.[102] Spatial-temporal clustering was reported for GCS[86] while temporal clustering was reported for PR.[100,103]

We, therefore, have evidence that these rashes can be contagious. To ascertain how contagious they are and to discover the routes of spreading the microbes we need more epidemiological data from a large number of patients with high homogeneity.

Treatment trials

Treatment trials can be conducted even if the underlying pathogenesis of a disease is not completely understood 104. For GCS, no systematic treatment trial was reported, and treatment consensus was not reached from case reports.[17,18,20,41,44,105-108] No randomized treatment trial was reported for APE, EP, and PPGSS.

For PR, various approaches have been adopted, including sunlight,[109] ultraviolet radiation,[110] non-antiinflammatory antibiotics,[111] antiinflammatory antibiotics,[36-39,108] antiviral agents,[36] topical and systemic histamine antagonists,[112] topical and systemic corticosteroids,[100,113] topical soothing lotions,[108,113] emollients,[113] and herbal remedies.[113] One pseudo-randomized controlled trial (allocating patients to treatment and control groups alternatively instead of randomly)[39] and three randomized controlled trials (Saveleva and Selinski, unpublished data, 2008; and[114,115]).

Were retrievable in a Cochrane systematic review.[113] Inclusion criteria of all these studies varied, and none of the four trials provided adequate evidence for or against the effectiveness of erythromycin (Saveleva and Selinski, unpublished data, 2008; and[39]), systemic corticosteroids,[114] systemic antihistamine,[115] and glycyrrhizin (a herbal remedy)[115] in PR, partly due to the small number of patients, and partly related to imperfect methodologies.[113]

We, therefore, realize that many treatment modalities being used are not substantiated by evidence of their efficacy or their adverse effects. To obtain more evidence, treatment trials need to have more power.[113]

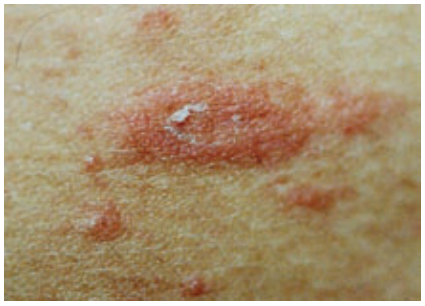

Figure 3. Typical herald patch in pityriasis rosea, showing collarette scaling configuration.

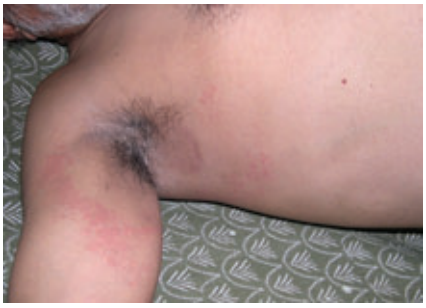

Figure 4. Typical unilateral latero-thoracic exanthema around right axilla in an adult Indian patient.

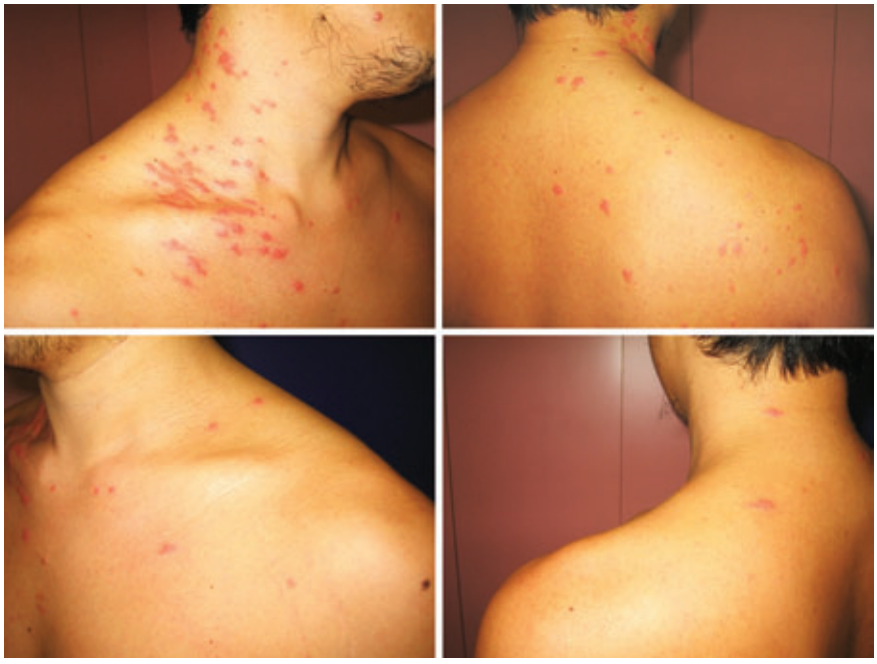

Figure 5. Erythematous papular lesions significantly more on the right neck and shoulder than on the left aspect of neck and left shoulder of a man with asymmetric periflexural exanthema.

Number of patients, power, publication bias and meta-analyses

Most of the studies reviewed above include only a small number of patients. The results might bear low statistical power, low clinical significance, and high risks of type 1 and type 2 errors. Moreover, trials with small numbers of patients are less likely to be published in mainstream dermatology journals, leading to publication bias. If one performs a meta-analysis or systematic review with published studies only, one runs the risk of missing the seriousness of unpublished studies. This is why Cochrane Reviews welcome unpublished studies.[113] One study quoted in this article, for example, is still unpublished (Saveleva and Selinski, unpublished data, 2008).

With the risk that journals may not accept articles for publication, the conduction of small-scale studies should not be discouraged, as few data are better than no data, and aggregation of data from small-scale studies would form large pools of patients and control subjects.[116] With techniques to minimize publication bias,[117,118] conglomerated results can be powerful.

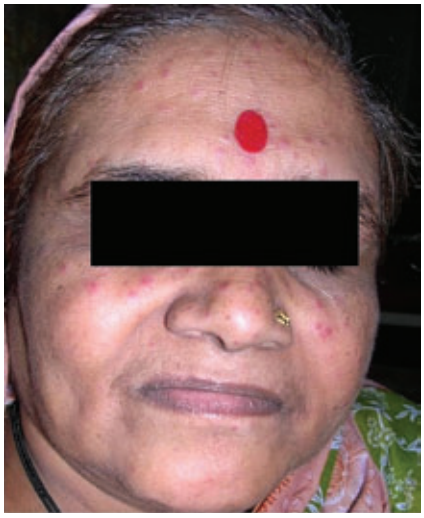

Figure 6. Typical lesions of eruptive pseudoangioma in an adult Indian patient.

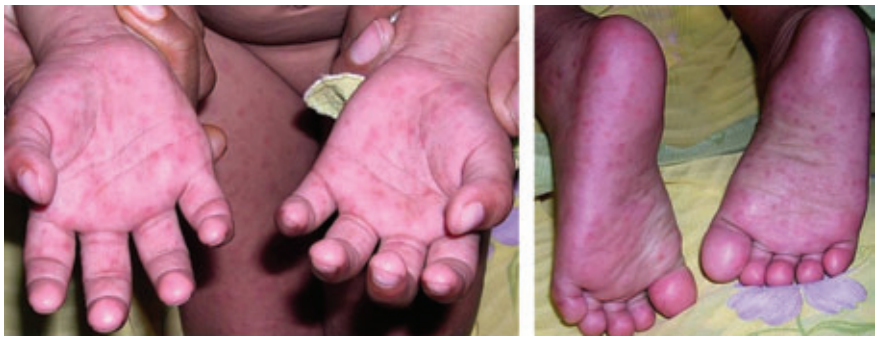

Figure 7. Typical lesions of papular purpuric gloves and socks syndrome in an Indian child.

However, from the brief review above, such aggregation of data is not yet possible, as the inclusion and exclusion criteria of various studies are different, leading to low homogeneity of the patient groups. The incongruent results for virological and epidemiological studies for PR, for example, might be partly related to the heterogeneity of the patients recruited. Imprudent use of meta-analyses would lead to invalid and incongruent conclusions, which might adversely affect patient care.

Diagnostic criteria

We, therefore, propose validation of DC as one of the priorities for future studies. We listed the currently working versions of our DC for GCS and PR in Table 1 and Table 2. The criteria for GCS were validated at two geographical locations,[119,120] while the criteria for PR were validated in one geographical location only.[121] These criteria are by no means finalized, and are to be further validated for different populations. Details of our reasons for advocating these DC are set out below.

Reasons for diagnostic criteria

High dependence on clinical diagnosis

GCS, PR, APE, ER, PPGSS and related exanthems are diagnosed clinically. Serological investigations mainly serve to exclude important differential diagnoses. Underlying factors such as diabetes mellitus or HIV infection should be evaluated if clinically appropriate. Skin scrapings for potassium hydroxide smear and fungal culture might exclude tinea corporis. Dermatoscopic examinations exemplify tiny clinical signs.[122] Lesional biopsy is too invasive and unnecessary for most patients with these exanthems. If performed, histopathology and immunohistochemical staining can substantiate, but cannot prove, a viral etiology.[123] Clinical photography documents changing signs[124] and may provide a platform for telemedicine.[125]

As investigations only assist in making a diagnosis, we have to depend on the clinical judgment of clinicians, which can vary widely. DC might help unify the reliability of diagnosis by different clinicians.

Clinical features in different populations

For different populations, these rashes can vary in the extensiveness,[87,88] distribution,[87] color,[91] and post-inflammatory hyper- or hypopigmentation.[87,88] One dermatologist might not be expected to be fully equipped to diagnose all variants of these rashes for different populations. DC would offer dermatologists and other clinicians systematic and objective diagnostic tools for different populations.

Different inclusion and exclusion criteria for different studies

Varying inclusion and exclusion criteria have been adopted in different studies.[113] This is most prevalently seen for PR. Most studies exclude rashes likely to be caused by medications,[45,73,77,113] but not all.[115] Some studies explicitly included patients with atypical rash,[73,78,79,114] some studies excluded patients with atypical features (Saveleva and Selinski, unpublished data, 2008) while other studies did not mention whether atypical rashes were included or excluded.[115] It is also not known how *atypical* a rash is to be considered for patients to be excluded.[113]

The level of invasiveness also varies across the studies for PR. In some studies, lesional biopsy was performed for all patients.[114] However, the need for lesional biopsy has been challenged.[113] Moreover, compulsory lesional biopsy might lower the rate of recruitment.[113] If a DC is used, the patients recruited will be more homogenous, and invasive procedures can be minimized.

For clinical and investigational studies, DC could serve as the basis of the inclusion criteria. Other qualifications such as demographic data can then be added on top of the DC. Not fulfilling the DC would raise concerns for exclusion, with other parameters such as drug intake or pregnancy being inserted as the exclusion criteria.

DC would assist in epidemiological studies and help obtain a homogeneous group of patients for proposed studies. For these studies, it would be logical to consider the DC as a primary endpoint. Otherwise, the collection of patients will be very heterogenic. For studies with diagnoses made by different investigators or clinicians, the sensible application of DC would provide a greater homogeneity among the recruited subjects.

Confusing terminology

GCS was first described in 1967.[1-3] The disease qualified as *non-relapsing, non-itching, monomorphic erythemato-papular dermatitis limited to the face and limbs… always associated with an acute hepatitis, with hepatitis B antigen in the serum and with a reactive reticulohistiocytic lymphadenitis*.[121] The initially described children were all anicteric.[1-3] However, icteric variants soon emerged[122,123] and whether this was the same disease was debatable.[124] An attempt was also made to separate *Gianotti syndrome* with vesicles from *Gianotti disease* without vesicles.[125]

On adult cases being reported,[126] the term *Gianotti disease* was adopted to describe adult cases. It was then believed that HBV led to different signs for children and adults.[21] In view of this, Gianotti himself clarified that GCS should continue to be known as *papular acrodermatitis of childhood*,[127] thus excluding adults.[21,126] He also summarized GCS *as an infectious disease of childhood, of low infectivity, fairly widespread, and characterised by: (1) Non-relapsing erythemato-papular dermatitis localised to the face and limbs, lasting about 3*

weeks. (2) Paracortical hyperplasia of lymph-nodes. (3) Acute hepatitis, usually anicteric, which lasts at least 2 months and may progress to chronic liver disease....[127]

However, it was later suggested that the term *Gianotti-Crosti syndrome* should be used for all adult and children patients irrespective of etiology, while *Gianotti disease* should be used if the cause was HBV infection.[19-21]

Today, *GCS* and *papular acrodermatitis of childhood* are considered synonymous.[19-21] For infants, *GCS* might be used, but *infantile papular acrodermatitis* is usually preferred. The rash in adults is being called *GCS in adults*,[114,115] with the term *adult papular acrodermatitis* not usually used.[114,115] More confusingly, the vast majority of patients with GCS today do not have acute hepatitis.[42-46,114,115]

For PR, after the original description by Gibert CM in 1860,[4] a similar rash *pityriasis circiné et marginé of Vidal* was described.[4] It was argued whether the latter was a variant of PR merely running a longer course, with fever and larger lesions often localized at the axillae or groins, or whether it was a new clinical entity.[4,84,128,129] Another term *pityriasis circinata et maculate* soon surfaced as a variant, but was later referred to as being synonymous to *PR*.[4] The medical literature today still embraces the entities *pityriasis rosea of Vidal*,[130,131] *pityriasis rosea of Gibert*,[132-136] and *pityriasis rosea circinata*,[137] all being synonymous of PR.

APE was originally described by Taïeb *et al.* in 1993,[8] with ULE first described by Bodemer and de Prost in 1992.[138] It was not until 1995 that researchers postulated that APE and ULE were the same disease.[17] With this debate still continuing, patients with a variant of ULE, namely UME, have been described.[10] UME bears little resemblance to APE, as it is not *peri flexural* at all. More studies should, therefore, be performed on the symptomatology of APE, ULE, and UME. Until then, we might have to tolerate these confusing terminologies.

There is no confusion in the naming of EP. However, whether EP is a homogenous disease or not is being debated. Owing to a wide range of rashes that differ in their contact history and disease duration, it has been suggested that EP is just a rubbish bin diagnostic label for non-specific viral exanthems.[52]

The term PPGSS is used whether it is related to HB19EV,[53-55] other viruses,[56-59,139,140] or other causes such as drugs.[141] The nomenclature does not change when PPGSS coexists with other cutaneous diseases[142] or in immunocompromised patients.[143] However, the wide variation in the number of words and hyphens defies seamless electronic indexing and searches, and standardization is needed.

DC will unify the terminologies of these rashes, making diagnostic labels clear and electronic searches much easier.

Table 1. Proposed diagnostic criteria for *Gianotti-Crosti syndrome*.[114,115]

A patient is diagnosed as having Gianotti-Crosti syndrome (GCS, or papular acrodermatitis) if:
1. on at least one occasion or clinical encounter, he/she exhibits all the positive clinical features;
2. on all occasions or clinical encounters related to the rash, he/she does not exhibit any of the negative clinical features;
3. none of the differential diagnoses is considered to be more likely than GCS on clinical judgment;
4. if lesional biopsy is performed, the findings are consistent with GCS.
The positive clinical features are:
1. monomorphous, flat-topped, pink-brown papules or papulovesicles 1-10mm in diameter;
2. at least three of the following four sites involved: (1) cheeks, (2) buttocks, (3) extensor surfaces of forearms, and (4) extensor surfaces of legs;
3. being symmetrical;
4. lasting for at least ten days.
The negative clinical features are:
1. extensive truncal lesions;
2. scaly lesions.

The differential diagnoses are: acrodermatitis enteropathica, erythema infectiosum, erythema multiforme, hand-foot-and-mouth disease, Henoch-Schönlein purpura, Kawasaki disease, lichen planus, papular urticaria, papular purpuric gloves and socks syndrome, and scabies.

Table 2. Proposed diagnostic criteria for pityriasis rosea.[116]

A patient is diagnosed as having pityriasis rosea if:
1. on at least one occasion or clinical encounter, he/she has all the essential clinical features and at least one of the optional clinical features;
2. on all occasions or clinical encounters related to the rash, he/she does not have any of the exclusion clinical features.
The essential clinical features are:
1. discrete circular or oval lesions;
2. scaling on most lesions;
3. peripheral collarette scaling with central clearance on at least two lesions.
The optional clinical features are:
1. truncal and proximal limb distribution, with less than 10% of lesions distal to mid-upper-arm and mid-thigh;
2. orientation of most lesions along skin cleavage lines:
3. a herald patch (not necessarily the largest) appearing at least two days before eruption of other lesions, from history of the patient or from clinical observation.
The exclusion clinical features are:
1. multiple small vesicles at the centre of two or more lesions;
2. two or more lesions on palmar or plantar skin surfaces;
3. clinical or serological evidence of secondary syphilis.

Wide spectrum of clinical features

For GCS, apart from anicteric[1-3] and icteric[122,123] forms, rashes with and without vesicles[125] were described. The signs are different for children and adults.[21] The size of papules and papulovesicles varies significantly.[144] The density of the papulovesicles or papules also varies widely according to the various body parts.[145,146]

Lymphadenopathy was present in around 30.8% of all patients with GCS.[147] When they do exist, there is a wide variation in sites and sizes.[148] Hepatomegaly was one of the cardinal features originally described.[1-3] However, it was found to be present in only 3.8% of patients in a more recent case series.[147] The duration of GCS can be extremely short or long. Although most children recover in 2-12 weeks, durations of five days and up to six months have been reported,[148] leading to suspicions of whether the same disease is being described; Gianotti mentioned *about three weeks*.[127] These variations make differentiation between GCS and its differential diagnoses a challenging task.[114,115] It is believed that it is not possible to reliably differentiate GCS clinically, whether it is due to HBV infection or not.[149] However, concomitant cutaneous signs of HBV infection complicate the clinical picture.[150-152]

For PR, the rash morphology can be vesicular,[153-157] purpuric,[157,158] hemorrhagic,[159] or urticarial.[160] The lesions can be gigantic or papular in size.[161] The distribution is highly

variable, with the classical rash affecting mainly the trunk and proximal aspects of all four extremities symmetrically, and variants with distal extremities being affected most (*PR inversus*),[162] restricted to the shoulders and the hips (*limb-girdle PR*),[163] or unilateral,[164,165] The number of lesions in PR can be at the extremes, known as *localized PR* with only 1-2 lesions[166] and *papular PR* with hundreds of lesions.[161] Involvement of special sites, such as the scalp,[128] eyelids,[128] penis,[129] and oral cavity,[167,168] defy easy diagnosis.

For APE, the lesions can be strictly asymmetrical[118] or nearly symmetrical.[169] Most rashes, being *peri flexural*, do not touch the midline. However, variants can touch the midline,[170] Lesions can be morbilliform, eczematous, a mixture of both,[171] lichenoid,[118] or scaly.[172] Associated axillary lymphadenopathy can range from severe[173] to almost undetectable.[118]

Distribution of lesions in EP could range from diffuse to fairly localized.[50,52] Lesions might be angioma-like[174,175] or telangiectasia-like.[50] They can be blanchable[176] or not blanchable.[50] A halo surrounding individual lesions is classical,[50] although it is absent in some cases.

For PPGSS, concomitant oral ulcers are considered classical. However, these can be completely absent.[177,178] The oropharynx could be swollen with a risk of asphyxia,[179] leading to a suggestion that PPGSS is not merely a cutaneous eruption. Involvements of the lips, chin, perioral regions, and neck are also highly variable.[14,179-181] It is said that where perioral lesions exist, HB19EV is likely to be involved, although this is not yet generally accepted.[180] In any case, perioral lesions can coexist with the *slapped-cheek* erythema in erythema infectiosum, thus confusing the dividing line between the two.[180] Atypical variants include a unilateral distribution,[182] involvements of the buttocks, genital, and axillary regions,[183,184] and large haemorrhagic bullae progressing to cutaneous necrosis and skin ulcerations.[185-187] Postmorbid states are usually scar-free,[14] but thick black eschars have been reported.[185]

With the wide variation in the manifestations, diagnosis is challenging, and is highly dependent on the individual experience of the clinicians. DC would make diagnoses more reliable.

Clinical audits

With DC, clinical audits for these rashes can be validly performed to evaluate the standard of medical care.[108,188] Changes can be made based on findings of the audits to improve the quality of care. The standards in making a diagnosis[189,190] and the standard of the laboratories in substantiating or refuting the diagnoses[191,192] can also be conducted and reported. This is possible only when there is a high homogeneity among the patients.

Clinical decisions

Let us examine a hypothetical case of a boy with suspected PPGSS being admitted into the pediatric ward. He may[53-55] or may not[56-59,193] be suffering from HB19EV infection. Serological and polymerase chain reaction investigations would be arranged, the results of which would be available three days later. Pediatricians and dermatologists have different opinions concerning diagnosis, a well-documented scenario.[194]

To what extent should the boy be isolated before the laboratory results are available? A nurse serving the ward is now 12-weeks pregnant. She might contract the virus while discharging her usual clinical duties,[195] with risks of spontaneous abortion and fetal abnormalities.[196,197] Should she be reversely isolated, or how long should she be granted leave? Expertise from many different sources offer a response to these questions, but it is important to consider whether it is valid to apply a diagnostic label of PPGSS in the first place. DC could hasten and facilitate this process.

Disease surveillance

From community and public health perspectives, surveillance of these rashes is important as the viral etiologies, clinical significance, and the rates of complications are still unclear.[198-200] HB19EV infection, for example, might lead to erythema infectiosum, PPGSS, or other clinical presentations. Asymptomatic virus shedding is common.[201] Its significance might be lower for Caucasian populations. For populations with high prevalence of congenital hemoglobinopathies, namely thalassemias, sickle-cell disease, or congenital spherocytosis, a rise in the incidence of PPGSS might signify escalating prevalence of HB19EV infection in the community[202] and, therefore, actions might have to be taken to detect and prevent aplastic anemia.

Limitations and pitfalls

First and foremost, clinical experience is a valuable attribute of the clinician in whichever branch of medicine he is practising. DC cannot replace the clinical acumen of clinicians. For some clinicians, making spot diagnoses not referring to DC might be easier. Some clinicians might apply the DC improperly and come to the wrong conclusions. On the other hand, the clinical acumen of some experienced clinicians might benefit from incorporating DC.

Clinicians should not depend entirely on DC in the face of incongruent clinical signs, when investigation results are incompatible, and if the expected clinical outcomes are not achievable. Otherwise, necessary interventions could be delayed.[203,204] Moreover, clinical features of these rashes might alter with time and with different populations. Plans to validate and re-validate DC should be in place before they are put into clinical or academic use. It would also be important if a commission of experts could collaborate in drafting and validating individual DC.

Furthermore, it would be ideal if such DC presents a sizable number of clinical photographs showing both typical and atypical exanthems. Dermatology is virtually an image-based speciality. More images will enhance the learning for non-dermatologists and dermatologists in training. For experienced dermatologists who have probably seen a number of atypical manifestations for each exanthem, the inclusion for more images will help delineate atypical exanthems from other differential diagnoses. One of the limitations in this article is that clinical photos are inadequate, as we are discussing several diseases. We shall tackle this limitation in future publications covering DC of individual diseases.

Patients and parents of patients can be very anxious while dealing with medical terminologies for these rashes[34,35] A sheet of DC means nothing to them, and it is the privilege as well as the responsibility of caring physicians to explain the diagnoses to them, communicate openly with them,[205] allay their fears[35] and heal them.

Conclusions

Rashes suspected to have a viral etiology may be much more common than generally believed. They might cause significant morbidities and have an impact on the quality of life of patients. The associated viral infections may lead to long-term complications which are still unknown to us. Investigations on the viral etiology, immunopathogenesis, descriptive epidemiology, analytical epidemiology, and treatment trials are important. However, diagnoses are often made clinically. Variants of these rashes are common, and the terminologies to describe these rashes are confusing. Published results from different studies are often conflicting.

Different studies adopt highly variable inclusion and exclusion criteria while recruiting patients. This may be part of the reason for the incongruence of published results. The number of patients in many studies is small. The power of their results is low. Studies with few patients might not be published in mainstream dermatology journals, leading to publication bias. Meta-analyses could be conducted to increase the statistical power and thus the clinical significance of these results. Adjustment methods are also in place to minimize publication bias. However, a prerequisite is that the patient populations are homogenous, which they are not for most published studies.

We suggest that future researchers might consider establishing and validating DC for these rashes. Apart from the benefits of DC for clinical and research purposes, these criteria might also prove themselves a resource for clinical audits and disease surveillance. We also encourage ongoing small-scale investigations if the investigators are unable to gather data from large population pools. However, the recruited patients in these investigations should be as homogenous as methodologically feasible with a view towards future aggregation of data with other studies. DC would be one of these methodologically feasible agendas.

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