Differential Diagnosis of Viral Exanthemas

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Abstract: This article describes the differential diagnosis of maculopapular rashes, which can be divided into three large groups: classic rashes, nonspecific rashes and paraviral eruptions, the last two of which can be grouped together as atypical rashes.

The differential diagnosis of maculopapular rash depends on the setting and the percentage of the population vaccinated. The diagnosis is broad and includes infectious processes and other etiologies. A correct diagnostic orientation requires the availability of the relevant epidemiological data which will aid the suspicion of a specific etiology.

Keywords: Measles, Rubella, Scarlet fever, Roseola, Infectious mononucleosis, Erythema infectiosum, Paraviral eruption.

INTRODUCTION

Maculopapular rashes can be divided into three large groups: classic rashes, nonspecific rashes and paraviral eruptions, the last two of which can be grouped together as atypical rashes.

The six classic rashes are measles, rubella, scarlet fever, exanthem subitum, erythema infectiosum and varicella. All, except varicella, are maculopapular and can thus be considered within the same differential diagnosis. They are named classic rashes due to a series of differential characteristics that allow them to be distinguished. However, on many occasions, the differences between them and their differentiation from other processes is not so clear. To a large extent, the differential diagnosis of maculopapular rash depends on the setting and the percentage of the population who are vaccinated. In an English study between 1996 and 1998, with vaccination coverages for measles and rubella of > 90%, no case of measles or rubella was found in 195 children with morbilliform rash [1]. The etiology was determined in 48% of cases, with the most-frequent agents being parvovirus B19 infection (17%), group A Streptococcus (15%), human herpes virus (HHV)-6 (6%), enterovirus (5%), adenovirus (4%) and group C Streptococcus (3%). In 52% of cases there was no evidence of infection. In contrast, in a Brazilian study carried out between 1994 and 1998 after a mass vaccination programme carried out in 1992 in children aged 9 months to 14 years, the most-frequent cause of morbilliform rash was dengue fever (33%), rubella (20.2%), parvovirus B19 (9.2%), measles (6.7%) and HHV-6 (2.1%) [2]. Most cases of measles were diagnosed in adults.

With respect to atypical rashes, an Italian study of 112 patients (78 adults and 44 children) with rash not compatible with any of the classic rashes identified the causal agent in 76 (68%) cases, with the most-frequent causes being viruses (28.6%) and drugs (22.3%) [3]. In macular or maculopapular rashes, the type of rash most-frequently found (66.1%), the main causes were drugs (18.7%) and viruses (17%).

With respect to measles and rubella, the differential diagnosis should be made with other infectious exanthematic diseases, drug reactions and Kawasaki disease.

In our setting, Kawasaki disease is undoubtedly, one of the processes that may most often be confused with measles. It normally presents in children < 5 years of age and is diagnosed by high fever for > 5 days with a bad response to antipyretic agents and four of the following signs: polymorphous maculopapular rash, involvement of the hands and feet (early edema and reddening or late desquamation), enanthema (cracked lips, pharyngitis or strawberry tongue), bulbar conjuntivitis not associated with exudates and unilateral cervical lymphadenopathy >1 cm. The diagnosis should always rule out other etiologies. There are usually early (elevated leukocyte count and acute phase reactants) or late (thrombocytosis) analytical alterations. The rash may be practically indistinguishable from measles, although it may also be erythematosus, urticariform or scarlatiniform. Characteristics which clearly differentiate Kawasaki disease from measles are the usual absence of Coryza and the onset of rash in the extensor surfaces of the limbs with later propagation to the trunk. Since Kawasaki disease may result in coronary aneurysms, physicians should be alert to its possibility, as early treatment with intravenous gamma globulin reduces the rate of complications.

Drug reactions may present with confluent, normally-itchy maculopapular rash which may coexist with fever and other general symptoms such as arthralgia. Drug consumption suggests the possibility but there is no confirmatory test and therefore the diagnosis is often difficult, as some viral rashes (including measles and rubella) may have a similar

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1875-0354/10

presentation. A good response to withdrawal of the drug and negative test results support the diagnosis.

Infectious processes that should be considered in the differential diagnosis of maculopapular rashes include viruses (measles, rubella, HHV-6, parvovirus B19, enterovirus, Epstein-Barr virus, adenovirus, dengue fever) and bacteria (*Streptococcus pyogenes*) (Table **1**) [4]. Measles is characterized by the four accepted clinical periods, with rising fever, profuse Coryza, disappearance of Köplik spots and morbilliform rash with onset in the retroauricular region which, within three days descends to the rest of the face, the trunk and the limbs.

Rubella is characterized by the triad of low-grade fever, swollen and tender glands and maculopapular rash, which is less intense than that of measles, with onset in the face and trunk and rapid progression to the limbs within 24 hours.

Table 1.

Disease	Incubation Period	Prodromal Period	Characteristics of the Rash	Desquamation	Characteristic Signs
Measles	8-12 days	Fever, cough, coryza, conjuntivitis. Duration: 3-4 days	Rash: maculopapular, confluent. Extends from the face to the trunk and limbs. Colour: red-purpura. Duration: 5-6 days	Furfuraceous. Palms and soles do not present desquamation	Köplik spots in oral mucosa
Rubella	16-18 days	Malaise, low-grade fever, coryza, conjuntivitis. Duration: 1-5 days	Rash: maculopapular, non-confluent. Extends from face to trunk and limbs. Colour: red-pink. Duration: 2-3 days	No	Lymphadenopathy (retroauricular and suboccipital) Arthritis and arthralgias (adult)
Scarlet fever	3-5 days	Fever, pharyngitis, vomiting. Duration: 12 h - 2 days	Rash: punctiform, erythematosus and rough. It respects the perioral triangle. Onset and predominance in skinfolds. Confluent. Colour: red. Duration: variable, sometimes very brief.	Laminar, affecting hands and feet.	Tonsillitis. Cervical adenopathies. Strawberry tongue
Exanthem subitum	5-15 days	High fever. Duration: 3-4 days	Rash appears when fever disappears: discrete maculopapular. Onset in thorax and trunk, progression to face and limbs. Non-confluent. Colour: pink-reddish. Duration: 2 days	No	Irritability. Occipital adenopathies
Erythema infectiosum	5-10 days	No	Indurated erythema in cheeks. Rash: symmetrical maculopapular rash in the extensor face of upper and lower limbs. Confluent. Colour: red-violet. Duration: 5-10 days (recurrences)	No	Erythema in cheeks
Enterovirus infections	Varies according to the agent, normally 3-5 days	Variable	Rash: maculopapular discrete, Non-itchy and generalized (aspect similar to rubella)	No	Aseptic meningitis
Infectious mononucleosis	4-6 weeks	Prolonged fever. Duration: 6-10 days	Rash: may manifest in various forms. More frequent after taking ampicillin.	No	Membranous tonsillitis. Lymphadenopathy. Hepatosplenomegaly.

Table. **1**. Adaptation (with permission) from: Barrabeig I, Casanovas JM, Domínguez A, García JJ, Sala P, Torner N, Van Esso D, Salleras L. L'eliminació de la rubèola a Catalunya per a l'any 2005. Bases científiques i programa. Barcelona: Quaderns de Salud Pública, Departament de Sanitat i Seguretat Social, Generalitat de Catalunya, 2002 [4].

The glands are painful in the retroauricular, posterior cervical and retro-occipital regions. Forchheimer's sign (petechiae in soft palate) may sometimes be observed.

HHV-6 presents with sudden rash, although the profile may sometimes be similar to measles, with fever rash, cough, conjuntivitis and coryza. In a UK study of 103 children with a clinical diagnosis of suspected measles or rubella, in which measles, rubella and parvovirus B19 were ruled out by serology, 85% of cases had HHV-6 antibodies, of which 40% had a low affinity, indicating recent infection [5].

Parvovirus B19 and *Streptococcus pyogenes* are possibly the most-frequent causes of morbilliform rash in our setting. Both pathogens may present, like measles, signs of infection of the upper respiratory tract, cough and mucosity, although conjuntivitis is less frequent. Parvovirus B19 causes erythema infectiosum. However, it may also present different clinical profiles ranging from asymptomatic forms to aplastic crisis, morbilliform rash with fever or papular-purpuric gloves- and-socks syndrome. *Streptococcus pyogenes* causes scarlet fever, characterized by high fever, tonsillitis and a rough, erythematosus micropapular rash, predominantly in the skinfolds, with onset in the neck and progression to the limbs. The perioral region (triangle of Filatov) is respected. It may present with Forchheimer's sign and is accompanied by strawberry tongue and terminates with furfuraceous desquamation 7-10 days after onset of the rash.

Other infectious agents may cause nonspecific rashes that can occasionally be confused with the classic rashes. They are generally non-itchy maculopapular rashes, predominantly in the trunk and limbs and accompanied by the absence of malaise and few other symptoms. However, the same rash may be caused by different viruses and the same virus may cause different types of rash.

Enteroviruses usually cause fever and rash with onset in the face and progression to the trunk and limbs. The rash is normally pink, with small maculopapules and may coexist with petechiae. The infection typically occurs in the summer and may occasionally result in concomitant aseptic meningitis.

The Epstein Barr virus is the main causal agent of infectious mononucleosis. Clinical manifestations range from asymptomatic in the youngest children to fever with tonsillitis, adenopathy and hepatosplenomegaly. There may be a pink maculopapular rash in the thorax and abdomen in up to 20% of children with mononucleosis, especially if beta-lactam antibiotics (amoxicillin and ampicillin) are administered concomitantly. Adenoviruses may cause different types of rashes, which are normally reddish and maculopapular. They may cause high fever, frequently with altered analytical parameters (leukocytosis and increased C-reactive protein), tonsillitis, conjuntivitis, adenopathies and pharyngo-tonsillitis which may frequently lead to difficulties in the differential diagnosis, especially with Kawasaki disease. Finally, Dengue fever is suspected in our setting only in patients with a history of recent travel to an endemic region during the rainy season. It presents with an influenza-like profile with a maculopapular morbilliform or scarlatiniform rash. The differential diagnosis with measles and rubella should be made, since Dengue fever is often common in regions where these diseases are endemic.

Finally, paraviral eruptions should be considered in the differential diagnosis. These are rashes that, like the classic rashes, are also characteristic, but are not due to the direct cytopathic effect of the virus but rather to a possible immune response of the host to the presence of virus in the skin. In addition, viruses are not the only causes of rash, since other stimuli may also cause their appearance [6]. Paraviral eruptions with a well-established viral etiology include Gianotti-Crosti syndrome (papulovesicular acrodermatitis), pityriasis rosea and papular-purpuric gloves- and-socks syndrome. Gianotti-Crosti syndrome is characterized by pink, symmetrical, monomorphic papules measuring 1-10 mm in the cheeks, buttocks and extensor surfaces of the limbs. In paediatric patients, it is principally associated with the Epstein-Barr virus. Pityriasis rosea begins with a primary pink plaque measuring 2-10 cm. (herald patch) and progresses to a general rash, consisting of maculas, papules and plaques measuring 0.5-1.5 cm several days later. The rash is symmetrical and predominates in the trunk, following Langer's lines. It is associated with infection by the HHV-6 and HHV-7 viruses.

Papular-purpuric gloves- and-socks syndrome is characterized by edema and painful, itchy erythema in the hands and feet, which progresses to purpuric rash. It has been associated with parvovirus B19, Epstein-Barr virus and cytomegalovirus. Asymmetric periflexural rash is also considered a paraviral rash, although studies have failed to show a viral etiology. It is characterized by a micropapular rash with onset in the axilla which extends centrifugally forming eczematous plaques. After some days, the rash appears on the contralateral side.

In conclusion, the differential diagnosis of maculopapular rash is broad and includes infectious processes and other etiologies. A correct diagnosis relies to a great extent on the relevant epidemiological data, such as the setting and the percentage of vaccination of the population which enables one or another etiology to be suspected.

REFERENCES

[1] Ramsay, M.; Reacher, M.; O'Flynn, C.; Buttery, R.; Hadden, F.; Cohen, B.; Knowles, W.; Wreghitt, T.; Brown, D. Causes of morbilliform rash in a highly immunised English population. *Arch. Dis. Child*., **2002**, *87* (3), 202-206.

[2] Oliveira, S.A.; Siquiera, M.M.; Camacho, L.A.B.; Nogueira, M.; Spinetti, C.C.J.; Cubel, R.C.N.; Kwowles, W.; Brown, D.W.G. The aetiology of maculopapular rash diseases in Niterói, State of Rio de Janeiro, Brazil: implications for measles surveillance. *Epidemiol. Infect.*, **2001,** *127* (3), 509-516.

[3] Drago, F.; Rampini, P.; Rampini, E.; Rebora, A. A typical exanthems: morphology and laboratory investigations may lead to an aetiological diagnosis in about 70% of cases. *Br. J. Dermatol*., **2002**, *147* (2), 255-260.

[4] Barrabeig, I.; Casanovas, J.M.; Domínguez, A.; García, J.J.; Sala, P.; Torner, N.; Van Esso, D.; Salleras, L. The elimination of rubella in Catalonia by 2005. Scientific basis and program. Monographs of Public Health, Department of Health and Social Security, Generalitat de Catalunya: Barcelona, **2002**.

[5] Tait, D.R.; Ward, K.N.; Brown, D.W.G.; Miller, E. Exanthem subitum (roseola infantum) misdiagnosed as measles or rubella. *BMJ*, **1996**, *312* (7023), 101-102.

[6] Lipsker, D.; Saurat, J.H. A new concept: paraviral eruptions. *Dermatology*, **2005**, *211* (4), 309-311.

Received: November 16, 2009 Revised: November 25, 2009 Accepted: November 25, 2009