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Case Report

Probable griseofulvin-induced morbilliform exanthem: a case report

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KEYWORDS

Cutaneous adverse drug reactions, morbilliform exanthem, griseofulvin.

ABSTRACT

The administration of drugs in average doses for medical purposes may cause cutaneous and mucosal manifestations known as cutaneous adverse drug reactions, which are neither expected nor desired. These skin eruptions may be seen in both mild and severe forms and among them, morbilliform exanthems should be pointed out as these can be caused by the intake of drugs usually beta-lactam antibiotics; however, they can occasionally be induced by other drugs. Among these, as seen in the 10 years old male patient we present, some cases have been reported originating from the use of griseofulvin, an antimycotic widely used to treat mycoses due to Microsporum canis. The best therapeutic approach, and sometimes the only one, is the rapid suspension of the causative drug, which is usually enough to resolve the situation in a few days. In the case of our pediatric patient, the decision was taken to therefore discontinue the drug. Once the condition was overcome, it was concluded to refer him to the Division of Allergy and Immunology in the hospital as an essential aspect of medical practice in order to better specify our presumptive diagnosis of drug hypersensitivity.

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1. Introduction

The administration of medication in average doses may cause morphological and functional alterations of the skin, skin appendages and/or visible mucous membranes known as cutaneous adverse drug reactions (CADRs) that are unwanted and unexpected. These skin manifestations are within the most common side effects caused by drugs (1). These skin pathologies caused by drugs are numerous and most of the time they are benign, characterized by maculopapular exanthems, urticaria and angioedema syndrome, fixed erythema and photodermatitis. Along with these clinical pictures, there are other potentially serious prognostic ones, such as erythroderma, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome and toxic epidermal necrolysis (3). The most frequently involved drugs are antimicrobials, anticonvulsants and non-steroidal anti-inflammatory drugs (4). Cutaneous adverse drug reactions are seen more in immunocompromised children than in the general population for reasons that are not very well known. However, we may take into account various risk factors that probably coexist in these children, such as polytherapy, chronic or intermittent treatment with drugs, and metabolic or immunological alterations (5). In our Dermatology Department, we have seen in recent months several children with benign skin manifestations arising probably after drug administration, one of which motivates the presentation of this case.

2. Clinical case

Jorge B., 10 years old, with no relevant personal or family history, visited the emergency room of our hospital due to a pruritic rash of 48 hours of evolution. He was prescribed diphenhydramine and referred to our department. With reference to his history of the current illness, he reported having consulted a doctor two weeks earlier due to flaking of the scalp and he was diagnosed with tinea capitis. He was then prescribed griseofulvin to be taken orally. On physical examination, the patient was found to be in good general condition, afebrile, with generalized erythematous maculopapular rash with lesions of varying size and shape, some of them confluent, that had started on the trunk with rapid spread to the limbs accompanied by a lot of itching (Figures 1, 2 and 3). The rest of the physical examination was normal. With a presumptive diagnosis of drug-induced morbilliform exanthem, treatment with griseofulvin was discontinued, diphenhydramine replaced by hydroxycine in doses of 2mg/kg/day divided every 8 hours and a complete blood count, liver function test and viral serology were requested. In the 72-hour return visit, the reduction of the exanthem and disappearance of pruritus were observed. One week later in the follow-up of the patient, the rash had disappeared and the child had no itching, although there was fine peeling. The laboratory tests were within normal parameters, and the serology for Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Herpes Simplex Virus 1 and 2 was negative. He was discharged, we prescribed an oat emulsion and sent him to the Division of Allergy and Immunology to

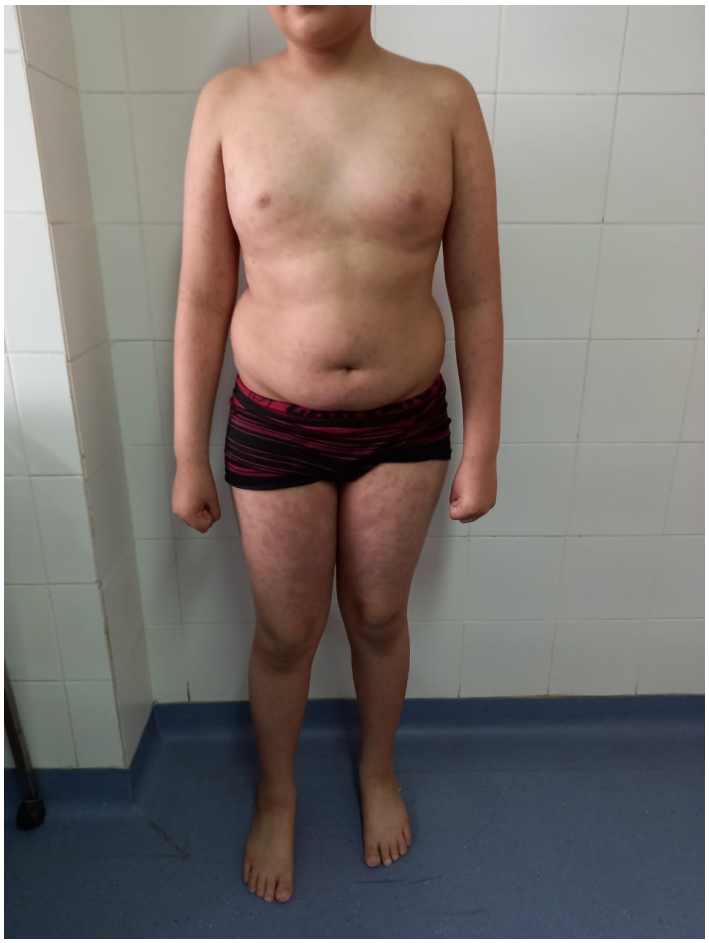

Fig. 1. *Disseminated maculopapular exanthema 14 days after the first dose of griseofulvin.*

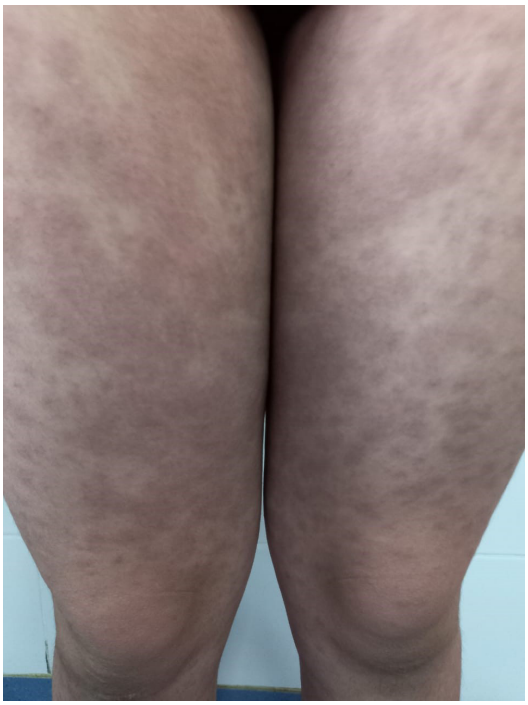

Fig. 2. *Thighs of the child showing red coloured maculopapular exanthema.*

confirm the presumptive diagnosis of hypersensitivity to griseofulvin .Upon being seen by the Allergist, it was believed that the rash was consistent with a Gell and Coombs type IVc reaction, linked to the ingestion of griseofulvin. Other in vitro or in vivo tests were not carried out, because griseofulvin testing is not standardized and because the resources are not available to evaluate T lymphocyte activation in vitro to confirm the causative drug. On the other hand, the allergists were hesitant about doing the provocation test with the drug, due to the fact that the rash was mild and it was not advisable to expose the child to the risk of a severe condition with re-exposure.

3. Discussion

Cutaneous drug eruptions are the most common types of adverse responses to drug therapy in children (6). The diagnosis may not be easy because the morphological appearance of the lesions is often similar to that of rashes of infectious origin. The most common clinical pictures of erythematous cutaneous drug reactions can be maculopapular morbilliform and scarlatiniform rashes (7). Other less common erythematous manifestations are rubeoliforme, multiform, eczematoid, psoriasiform, and lichenoid eruptions.

The most common drugs responsible for these outbreaks are beta-lactam antibiotics (4) and also but less frequently sulfonamides, phenytoin, carbamazepine, phenobarbital and non-steroidal anti-inflammatory drugs (NSAIDs), although virtually any drug can cause these symptoms (8). Therefore, taking this into consideration the fact that any drug can cause erythematous rashes, such as griseofulvin, we report the situation of the case of one young male patient who consulted our department (9). This patient, fourteen days before the outbreak, was receiving griseofulvin to treat tinea capitis and although this is not one of the drugs most commonly involved in cutaneous adverse drug reactions, there are several citations in the literature (10,11). The pathophysiology of morbilliform drug eruptions is currently unclear, although an immunological mechanism is probably involved. It is believed to be a type IV or a delayed T-cell hypersensitivity reaction, a belief supported by the finding of a CD4 (+) infiltrate in the skin biopsy and the presence of drug-specific T cells in lymphocyte transformation tests (12). CD8 T cells are also believed to play a role by migrating into tissues in order to act as the cytotoxic effector cell (13). When suspecting a drug rash, we should also take into

account the latency interval, which is the time elapsed from the start of drug administration and the appearance of the clinical picture, for erythematous cutaneous adverse reactions is within two weeks of starting drug use. This is the case of our patient who started taking griseofulvin two weeks before the outbreak manifested. It is important to clarify that in children previously sensitized skin lesions appear following re-exposure in less time, from a few hours to 7 days. Morbilliform exanthema is characterized by flat or slightly raised macules, 1 to 5 mm in diameter, pink or red in color, tending towards confluence, usually appearing on the upper part of the trunk, neck and face with successive centrifugal extension towards limbs, bilaterally and symmetrically, sometimes accompanied by low-grade fever and itching (14, 15). Our patient presented a typical bright red, maculopapular morbilliform drug eruption, as can be seen in figure 3. It is important to point out that sometimes, if the administration of the drug is not interrupted, erythematous cutaneous adverse reactions can evolve into an erythroderma with possible serious systemic complications. Given the high prevalence of viral diseases in children, differentiating between a drug rash and one of viral origin can be difficult, many times resulting in a true diagnostic challenge. This difficulty is exacerbated by the fact that the viral infection coupled with drug administration may increase the risk of a morbilliform drug eruption, since children frequently receive antimicrobials as an empirical treatment (16).

The diagnosis of CADRs cannot be based only on the history of the drug administration, which in the case of our 10-year male patient was approximately two weeks before. As to the cause of the disorder, it is essential to take into account the non-uniform morphology of the maculopapular lesions, more often due to the co-

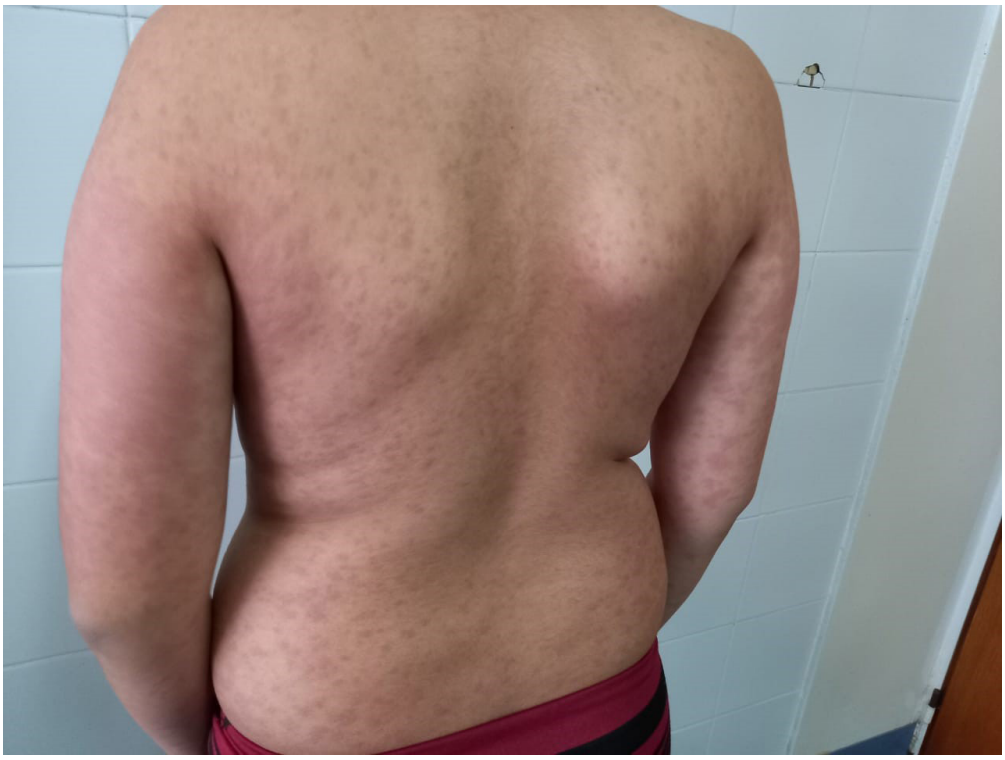

Fig. 3. *Back of the child showing multiple erythematous lesions.*

existence of morbilliform and scarlatiniform models, but also because of the presence of lesions resembling wheals or erythema multiforme, the red wine color and the symmetrical distribution of manifestations.

The prevalent onset on the trunk and subsequent rapid spread, pruritus, resolution with scaling pityriasis, general symptoms that are often absent, and negative microbiological and serological tests also support the drug-induced etiology. The involvement of the face, palms, and soles, as well as the presence of fever, malaise, rhinitis, odynophagia, enanthema, and lymphadenitis, are more indicative of viral or bacterial infection. In addition to infectious rashes, other differential diagnoses to consider include acute urticaria and food al-

lergies. In this regard, it should be remembered that our patient had no recent history of having ingested foods that could potentially trigger the rash nor did he present the typical hives of acute urticaria. An important aspect to bear in mind and possibly the best approach against a CADRs is the immediate suspension of drug administration (17) and the rash will generally begin to improve 48 hours after the drug is discontinued (18). Furthermore, symptomatic treatment can be carried out if the patient shows itching and first generation oral antihistamines such as hydroxyzine are the most effective means of symptom relief. Second-generation H1 blockers can be an alternative for cases with less itching, because they have a lower sedative effect compared to first-generation ones (19, 20). In some specific situations, either due to the magnitude of the outbreak or because the clinical picture progresses and becomes more severe, systemic corticosteroids may be beneficial (21). In our patient, hydroxyzine administered every 8 hours achieved prompt relief of pruritus. The rash, which is self-limited in itself, is usually resolved within 7 to 14 days after discontinuation of the causal drug (22). While the color of the erythema fades, a superficial pityriasis scaling is common, similar to that which occurs in rashes of infectious origin. In this phase of resolving the rash, the lesions can take on a brownish-brown color and persist for several months, especially in children with a high photosensitivity (23), although this does not seem to have occurred in our patient. In this resolving time of the disease, it is recommended to avoid the sun to accelerate the normalization of skin color and use emollients, which prevent skin dryness due to peeling. Once the episode is over, allergy tests should be performed to identify the responsible drug (24, 25).

In the child who is the subject of this presentation, the allergy department could not confirm the responsibility of griseolfulvin with laboratory tests, but shared our clinical suspicion. Our approach was to immediately suspend the drug and in just over a week the skin recovered its normal appearance although with fine flaking.

4. Conclusion

It is important to take into consideration that erythematous drug rashes are common in the pediatric practice. Although the usual drugs that trigger these disorders are beta-lactam antibiotics, other drugs can occasionally be the cause, as we believe occurred in this male patient with the use of griseofulvin. The immediate suspension of the drug is usually enough to resolve the outbreak in a few days. Although we could not confirm our clinical suspicion due to the allergy test, the child´s clinical picture, added to the history of ingestion of griseofulvin since two weeks before the onset, the lack of any other potential drug or dietary trigger, the negative serological screening and the rapid remission of the eruption upon discontinuation of the drug, strongly suggests griseofulvin as the probable cause of the eruption.

As mentioned before, there are several reports of skin reactions linked to the use of griseofulvin such as acute urticaria and Stevens-Johnson syndrome, but as far as we know, there are no reports of rashes similar to an infectious exanthema, which is why we decided to make this communication.

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DISCLOSURE

The author reports no conflict of interest.

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