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Case Report: True Drug Sensitization to Co-amoxiclav During Acute Infectious Mononucleosis

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Skin reactions following antibiotic administration amidst acute infectious mononucleosis (IM) were long thought to be exclusively a transient hypersensitivity reaction of the immune system, and further allergological testing was rarely conducted. This paper presents the case of a 19-month-old boy who developed a delayed-type hypersensitivity reaction to co-amoxiclav during acute IM. The case serves as a reminder that any new onset of rashes following antibiotic treatment should undergo detailed allergological testing until proven otherwise.

Keywords: DRUG HYPERSENSITIVITY; AMOXICILLIN CLAVULANIC ACID; INFECTIOUS MONONUCLEOSIS; DRUG ERUPTION

INTRODUCTION

Infectious mononucleosis (IM) is an acute, usually self-limiting disease caused by the Epstein-Barr virus (EBV) or the cytomegalovirus (CMV). In 4.2 to 13% of cases of acute IM, a rash can appear without concomitant drug or antibiotic use (1). Given the similar symptoms of acute IM with a bacterial infection, many patients in the acute phase receive antibiotics empirically. Antibiotic use during the acute phase of IM has been observed to raise the incidence of skin eruptions from 27.8 % to 69% (2, 3). Antibiotics associated with skin reactions like maculopapular exanthema, urticaria and petechial rash occurring within 5-14 days of antibiotic treatment include penicillin derivatives (most commonly ampicillin and amoxicillin), followed by cephalosporines (cephalexin and cefepime), sulfonamides, quinolones and macrolides (erythromycin and azithromycin) (4). Former consensus statements regarding skin reactions following antibiotic use during acute IM have frequently concluded that it merely represents a transient immunological reaction, not a true drug sensitization involving delayed-type hypersensitivity, making further allergological testing unnecessary (5). A growing body of evidence shows that true drug sensitization can develop and last undiagnosed if allergy examinations are not conducted (3, 6-9).

Recently, new concepts in understanding delayed-type hypersensitivity have emerged that propose the hapten and pro-hapten concepts, as well as the p-i (pharmacological interaction) concept, which all endeavour to explain the underlying mechanisms of drugs becoming immunogenic and triggering the innate, as well as the adaptive immune response (10-13). The hapten and pro-hapten concepts suggest that to become an effective immunogen, the drug must bind covalently to high-molecular-weight proteins, forming a hapten-carrier complex which later undergoes processing and presentation in antigen-presenting cells (APCs), or directly stimulates the innate immune system by binding to cellular protein receptors such as the Toll-like receptors (TLR). For example, drugs such as penicillin are intrinsically chemically reactive, making them prone to spontaneous covalent binding to other molecules (14). Pro-hapten does not share this kind of chemical reactivity; hence it must be metabolized into a hapten first and than act as

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described above (14, 15). The p-i concept is the most recent breakthrough observation regarding the pharmacological interaction of drugs with immune receptors, hence its name. It postulates that drugs that are otherwise chemically inert and cannot form a hapten-carrier complex, bind with low affinity to the T-cell receptor (TCR) in the presence of the MHC-molecule, which ultimately ends in T-cell activation and expansion, triggering the systemic immune response and manifesting most often in the form of a maculopapular rash (11). During the presence of acute IM, or in some cases, other viral diseases, it may happen that although quite a few TCRs possess the ability to interact with drugs, a lower threshold for eliciting activation of T-cells exists because they are already in an activated state (15). Evidence supporting this conclusion stems from the observation that in acute IM, the polyclonal activation of reactive T-lymphocytes creates an opportunity for some of these clones to begin initiating the subsequent immune response to the offending agent (3).

On the other hand, when the immune system is not in a heightened mode of reactivity, and the conditions for selecting reactive T-cells are no longer present, the low-affinity interaction of the drug and TCR is not sufficient to elicit the immune response as is the case during its florid viral phase. That can be tested later by conducting an oral provocation test with the offending agent, which often shows that true drug sensitization had not taken place. These kinds of transient hypersensitivity reactions are often seen in childhood (15).

Whether a true drug hypersensitization or a transient hypersensitivity reaction occur, depends on the affinity of TCR and the offending drug and the extent of T-cell expansion. Subsequently, the sufficient proliferation of drug-specific T-clones may ultimately lead to the development of true drug sensitization manifesting as a delayed-type hypersensitivity reaction. Furthermore, T-cell clones can also mediate humoral immune response with the simultaneous activation of B-cells, depending on the cytokine milieu present during the antigen-presentation process (15).

CASE PRESENTATION

A 19-month-old boy presented to our emergency department with a generalized erythematous rash involving the face, neck, chest, stomach, back, gluteal region and thighs (Figure 1). Facial edema was also observed. The rash was blanching, maculopapular, erythematous and sandpaper-like. His throat was erythematous with concomitant enanthema of the palate. Angular lymph nodes were enlarged and painful to palpation. The child was on the eighth day of antibiotic treatment with co-amoxiclav following an avulsion injury to his left thumb. During the last two days, he experienced a serous nasal discharge, loose stool and a temperature measuring 38°C in the ear. In the initial laboratory work-up, there was a slight increase in the C-reactive protein (10.8 mg/L), lymphocytosis, and increased ALT and LDH, measuring 60 U/L and 732 U/L, respectively. Eosinophilia was not observed. The child was admitted to the Pulmoallergology department and parenterally rehydrated, after which an antihistamine (desloratadine, 1.25 mg) and an intravenous corticosteroid (methylprednisolone, 15 mg) were administered. Antibiotic administration of co-amoxiclav was immediately withdrawn. Following this treatment, we observed a significant regression of facial edema and the rash. Serology tests for EBV, CMV and parvo B-19 were made and came back positive for EBV, indicating acute infection. The possibility of a delayed-type hypersensitivity reaction to co-amoxiclav during the acute IM was postulated, but further tests were needed. An LTT (lymphocyte transformation test) for co-amoxiclav was scheduled six

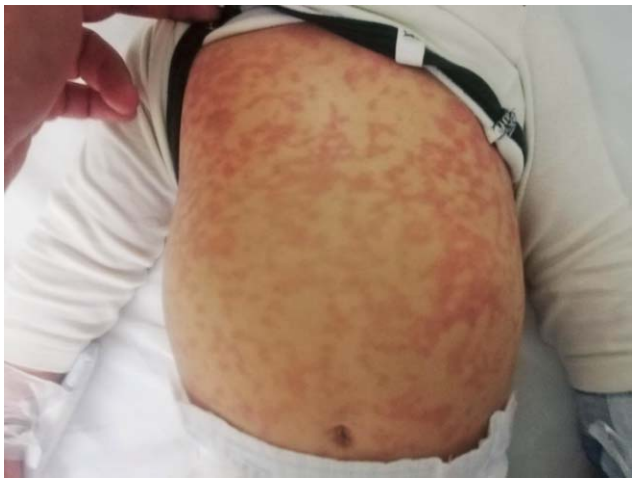

FIGURE 1. **Confluent erythematous rash of the trunk.**

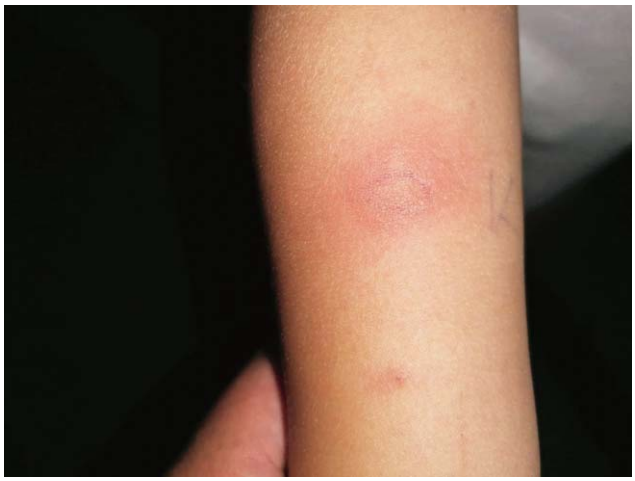

FIGURE 2. **A positive intradermal skin test following 22 h of the initiation of the test.**

weeks after the onset of the disease and came back negative (the stimulation index was <2.0, which is interpreted as a negative result (16)). Due to the COVID-19 pandemic, skin testing was conducted 10 months later. The skin prick-test for co-amoxiclav turned out negative, whereas the intradermal test (co-amoxiclav 20 mg/4mg/mL) was positive (an overall increase of the initial 3 mm papule diameter after administering 0.03 mL of the reagent solution was ultimately 3.5 mm, bringing the total wheal diameter to 6.5 mm, and therefore rendering the test positive according to the EAACI 2020 guidelines (17)) following 22 h upon initiation of the test (Figure 2). These results indicated a delayed-type hypersensitivity reaction to co-amoxiclav administration during the acute onset of IM.

DISCUSSION

Exanthematous drug eruptions are among the most common types of hypersensitivity reactions and occur in various shapes and forms, usually manifesting within approximately one week after drug initiation (18, 19). Although the exact pathophysiological mechanisms underlying these clinical manifestations are still not fully elucidated, the general opinion indicates either a transient loss of a tolerance state resulting in transient hypersensitivity or a truly delayed-type hypersensitization to an offending agent (6, 7).

We wanted to point out that contrary to previously popular opinion, true drug sensitization amidst a fulminant viral disease can also emerge, manifesting as a delayed-type hypersensitivity reaction. On account of circulating memory T-cells, the immune system can be triggered each time the offending drug is given. These cells are the main mediators of delayed-type hypersensitivity reactions (type IV), which are further classified into four subcategories, each with its own set of recruited immune cells and cytokine milieu (15, 20). It is worth pointing out that the provocation test was not administered in our case, considering we had proven true drug sensitization based on the patient's history, clinical evidence and positive IDT. To conclude with certainty whether this delayed hypersensitivity is transient or sustained, we can repeat *in vitro* (LTT) and *in vivo* tests (prick-test, IDT) in two to three years, and if they come back negative, an oral provocation test can be employed if the patient's parents provide consent.

Considering all this, it becomes clear that any rash linked to antibiotic use and during acute IM should undergo a further allergological examination to differentiate whether it is a transient immune reaction or a true drug hypersensitization.

As seen in our case presentation, a high index of suspicion is needed when dealing with patients with a history of acute illness, new onset of rashes and recent drug therapy. Given the diagnostic restrictions, concluding which type of T-cell-mediated immune response predominately affected the patient from our presented case was not possible. Had a skin biopsy been done, it might have elucidated some of these questions. Also, measuring the serum cytokines may have provided answers. Based on our clinical findings, *in vivo* testing, and similar literature reports, our final assumption is that either a type IVb or IVc reaction was triggered in our patient.

Nevertheless, early identification of IM amidst a new onset of the rash and a history of antibiotic use is paramount in planning further diagnostic evaluation regarding possible true drug sensitization and distinguishing it from a transient immune reaction.

CONCLUSION

Acute IM is a self-limiting viral disease that often gets confused with bacterial infection due to its nonspecific symptoms in the prodromal phase. Hence, many patients end up taking one or more antibiotics during the florid phase of the viral infection, which can then elicit various kinds of skin reactions. Although it is well known that the virus can interact with a drug and alter the immune system, these interactions were once thought to be transient. However, recent data show that persistent delayed-type hypersensitivity to an offending agent can develop, putting allergy work-up high on the priority list when dealing with IM patients who develop skin symptoms while taking these antibiotics.

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SAŽETAK

Reakcija odgođene preosjetljivosti na amoksicilin-klavulansku kiselinu u tijeku aktune infektivne mononukleoze

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Kožne reakcije u tijeku akutne infektivne mononukleoze, a nakon primjene antibiotika, dugo vremena smatrane su tek prolaznom reakcijom preosjetljivosti tada već ionako podraženog imunološkog sustava pa je daljnje alergološko ispitivanje rijetko bilo indicirano. U ovom prikazu slučaja riječ je o 19-mjesečnom dječaku koji je razvio reakciju odgođene preosjetljivosti na amoksicilin-klavulansku kiselinu tijekom akutne infektivne mononukleoze što bi nam trebalo služiti kao podsjetnik da svaka nova pojava osipa uslijed ili nakon primjene antibiotske terapije treba proći detaljno alergološko ispitivanje kako bi se utvrdilo stoji li u podlozi zapravo alergijska reakcija.

Ključne riječi: ALERGIJA NA LIJEKOVE; AMOKSICILIN-KLAVULANSKA KISELINA; INFEKTIVNA MONONUKLEOZA; TOKSOALERGIJSKI OSIP