

Amoxicillin Adverse Cutaneous Reaction Versus Post Streptococcal Vasculitis

Lymphocyte Transformation Test Solved the Question

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Abstract: In children, skin rashes are a frequent manifestation of infectious diseases, or they could also be the result of a drug hypersensitivity reaction, especially after antibiotic intake. We report the case of a 5-year-old girl investigated for a suspected post streptococcal vasculitis where differential diagnosis was improved by an allergy work-up and confirmed by lymphocyte transformation test.

Key Words: amoxicillin-clavulanic acid, children, lymphocyte transformation test, post streptococcal vasculitis, adverse drug reaction

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In the pediatric population, skin rashes are a frequent manifestation of infectious diseases, or they could also be the result of a drug hypersensitivity reaction, especially after antibiotic intake. Clinical features range from mild manifestations (eg, maculopapular exanthemas) to the severe cutaneous adverse reactions, which are rare and could be mostly drug-related but also determined by a combination of both infection and drug hypersensitivity.¹ These conditions belong to group IV according to the modified Gell and Coombs classification, where T lymphocytes are the most important key effector cells.²

We herein describe a case of drug hypersensitivity reaction caused by amoxicillin-clavulanic acid (AMX/CLV) and confirmed by lymphocyte transformation test (LTT), initially misdiagnosed as a postinfection vasculitis.

A 5-year-old girl was referred to the Rheumatology Unit of Meyer Children's Hospital for suspected streptococcal vasculitis. Medical history was remarkable for sore throat with a positive cultural swab for GABHS (group A beta-hemolytic *Streptococcus*) 3 weeks before the vasculitis onset. Therefore, she received a 10-day course of AMX/CLV, oral suspension. On the ninth day, an urticarial rash appeared, but therapy was continued along with antihistamine (HI) administration. The day after, she also developed hand and feet angioedema and, in the following hours, pain in her ankles and knees with difficulty in walking. She was administered histamine and steroids again for 2 days, but then

she developed a maculopapular exanthema with signs of vasculitis. A blood examination revealed C-reactive protein 2.13 mg/dL (normal value < 0.5), with blood count, coagulation, liver and renal function in normal range. Serology for Epstein-Barr virus, cytomegalovirus, chlamydia and mycoplasma were negative. Antistreptolysin O titer resulted 203 UI/mL (normal values < 200), and antideoxyribonuclease B (anti-DNase B) antibodies were negative. The patient reported intermittent, migratory joint pain at feet, ankles, knees and elbows, so ibuprofen therapy was started. Hip ultrasound showed mild joint effusion, and a cardiac examination excluded sign of valvular involvement. After 6 days, she received rheumatology evaluation, where no signs of arthritis and no signs of vasculitis have been detected. Laboratory examinations were repeated and did not show signs of inflammation, and Antistreptolysin O and anti-DNase B resulted 215 and 343 UI/mL, respectively (normal values < 200 UI/mL).

A presumptive diagnosis of a GABHS infection's complication was considered,^{3–5} but a moderate/severe potential AMX/CLV reaction could not be excluded. Thus, before proceeding with benzathine benzylpenicillin prophylaxis prescription, an allergy consultation was required.

The allergy work-up started with an intradermal test (IDT) with AMX/CLV at concentration 20 mg/mL according to standard procedures⁶ with readings at 20 minutes and at 24 and 48 hours. Skin testing was considered positive at immediate reading when the IDT was >3 mm from the initial wheal or when an increase in the diameter of the initial wheal was associated with a flare, together with a negative saline control result; at late reading, IDT was considered positive when erythema and/or infiltration appeared >24 hours. In vitro tests included assays for total serum and specific IgE (sIgE) to Penicilloyl G, Penicilloyl V, Ampicillin, AMX and Cefaclor, performed using ImmunoCAP (ThermoFischer scientific, Uppsala, Sweden). A value ≥0.10 kUA/L was considered positive.

LTT, able to measure the proliferation of serum T-cells when exposed to a specific drug, was additionally performed. Peripheral blood mononuclear cells were isolated using a Lymphoprep (Sentinel Diagnostic, Milan, Italy) density gradient followed by 2 washings with PBS (phosphate-buffered saline) at pH 7.2. Groups of 2×10^5 cells were cultured in triplicate in round-bottomed 96-well plates in complete medium plus 5% heat-inactivated autologous serum in a final volume of 0.2 mL for 5 days in the presence of 4 increasing doses of each beta-lactam antibiotic (penicillin 2.5–0.5–0.1–0.02 mg/mL, ampicillin 2.5–0.5–0.1–0.02 mg/mL, AMX 1–0.5–0.1–0.02 mg/mL and AMX/CLV 0.5–0.1–0.02–0.004 mg/mL) or medium alone as a negative control at 37°C in a 5% CO₂ humidified atmosphere. As positive controls, 2500 IU/mL recall antigen streptokinase (SK) and 1% vol/vol polyclonal activator phytohemagglutinin (PHA) were used. After 16-hour pulsing with 0.5 µCi HTdR per well (PerkinElmer, Waltham, MA), cultures were harvested, and the radionuclide uptake was measured

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TABLE 1. Elements That Could Help to Make a Differential Diagnosis Between a Complication of GABHS Infection and a Delayed Adverse Drug Reaction to AMX

	Complication of GABHS infection	Delayed adverse drug reaction to AMX
Consistent trigger	Pharyngitis with positive cultural swab for GABHS	Intake of AMX
Onset after trigger (infection/ drug assumption)	7–10 days	>1 hour
Clinical manifestation	Migratory arthralgia of lower large joints, signs of cutaneous vasculitis	Urticarial rash, angioedema, signs of cutaneous vasculitis
Blood examinations	Serologic evidence for antecedent GABHS infection	Positivity for AMX at LTT

AMX indicates amoxicillin; GABHS, group A beta-hemolytic *Streptococcus*; LTT, lymphocyte transformation test.

by scintillation counting. The stimulation index was calculated as the ratio between the radioactivity from stimulated cultures and that from unstimulated cultures. A stimulation index ≥ 3 was considered to be positive.⁷

In vivo and in vitro tests were all made 4 weeks after the reaction and after a complete recovery.

IDT and specific IgE for beta-lactams were negative. On the contrary, LTT showed high positivity for AMX with an SI of 58.9 at a concentration of 1 mg/mL and 48.3 at a concentration of 0.5 mg/mL.

The diagnosis of hypersensitivity reaction to AMX was thus confirmed and the patient was advised to avoid penicillins, including the prophylaxis with intramuscular benzylpenicillin.

In the article, a suspected complication of streptococcal infection was revealed to be a delayed adverse drug reaction to a beta-lactam. It could also be assumed that GABHS could have played a role in the pathogenesis of the reaction together with the hypersensitivity T-mediated reaction to AMX. Since the vivo tests were not informative, and the drug provocation test was judged not possible due to the risk of again triggering a potential similar reaction, allergy investigations led to the final diagnosis exclusively by performing LTT.^{8,9} Table 1 reported clinical signs and laboratory investigation results that can help to discriminate between a complication of a GABHS infection and a delayed adverse drug reaction to amoxicillin.

In conclusion, this case report underlies the utility of LTT in delayed cutaneous reactions. According to previous results and particularly in cases where the drug provocation test cannot be performed with the culprit because of the severity of the index reaction,¹ LTT seems to have a higher diagnostic performance than in

vivo tests. Limitations of LTT are related to the complexity of the procedure and the need for qualified laboratories and specialized personnel. Anyway, LTT should be a method in which to invest to better standardize it and not to confine it to only research purposes.

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