Clinical case

Delayed aminopenicillin reaction associated to human herpes virus 6 infection mimicking DRESS syndrome

Reacción tardía a aminopenicililina asociada con infección por el virus del herpes humano 6 que simula síndrome DRESS

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Abstract

Background: DRESS syndrome (rash with eosinophilia and systemic symptoms) is an uncommon and severe drug-induced reaction.

Clinical case: An 8-year-old boy was diagnosed with tonsillopharyngitis, and treatment with amoxicillin was started. One day later, he presented bilateral malar rash which evolved to generalized erythroderma in two days. He was referred to the emergency room and then he was discharged after the treatment with amoxicillin was discontinued. Five days later, he still had fever, progressive facial and acral edema, and ecchymotic lesions. The laboratory studies showed 6220 leukocytes/mm³ (970 eosinophils/mm³). The pharyngeal culture tested positive to human herpesvirus 6 (HHV-6). The fever, rash and edema disappeared with supportive measures. Based on the results of the allergy tests, a diagnosis of delayed reaction to aminopenicillin associated to HHV-6 mimicking DRESS syndrome was made, with the recommendation to avoid penicillin antibiotics.

Conclusions: The diagnosis of delayed reactions to aminopenicillin and DRESS syndrome requires a high index of suspicion in order to promptly withdraw the offending medication and to avoid delays in the diagnosis.

Keywords: DRESS syndrome; Amoxicillin; Human herpesvirus 6; Eosinophilia

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Background

DRESS syndrome (drug rash with eosinophilia and systemic symptoms) is a severe and uncommon drug-induced reaction and it is usually characterized by a long latency between the intake of the causative drug and the onset of the disease (2 to 6 weeks). Although it can be caused by several agents (like antibiotics), it was first and mainly reported to be linked to anti-epileptic agents. Amoxicillin is not usually reported as the primary causative agent despite its wide use in both adults and children.

Case report

An 8 year old boy with fever and a sore throat was diagnosed with acute tonsillopharyngitis, and treatment with amoxicillin was started (it had been previously well tolerated). One day later, he presented bilateral malar rash which evolved to generalized erythroderma in two days, with joint inflammation and a persistent fever. He was referred to the emergency room and then he was discharged after the treatment with amoxicillin was discontinued. Five days later, the patient still had a fever (39 °C) and increasing erythroderma, and he also presented progressive facial and acral edema, and linear ecchymotic lesions in the neck, armpits and groin. His body weight increased 1.2 kilograms in 2 days. The laboratory studies showed 6220 leukocytes/mm³ (970 eosinophils/mm³), with normal liver and renal function (alanine aminotransferase 19 IU/L, urea 17 mg/dL, creatinine 0.33 mg/dL). The pharyngeal culture tested positive to human herpesvirus 6 (HHV-6) (127.527 copies/100 cells by polymerase chain reaction). The patient was admitted in the hospital for two days, during which the fever, rash and edema disappeared with supportive measures. Ten days later, his blood tests were normalized (8150 leukocytes/mm³, 430 eosinophils/mm³). Specific IgE
to penicillin G, penicillin V, ampicillin and amoxi-
cillin was < 0.1 kU/L. An immediate reading of the
skin prick test and the intradermal test (IDT) to ben-
zylpenicilloyl-polysine (PPL), minor determinant
mixture (MDM), ampicillin (20 mg/mL), amoxicillin
(20mg/mL) and cefuroxime (25 mg/mL), turned out
to be negative. A delayed reading of IDT (48 hours)
tested positive to ampicillin (4 mm) and amoxicil-
lin (6 mm), but negative to cefuroxime (0 mm). A
patch test (with vaseline) turned out to be positive to
amoxicillin 10% (+), ampicillin 10% (+), cefuroxime
20% (+), and amoxicillin-clavulanic acid 10% (+),
but it tested negative to cefuroxime 10% (−) at 48
and 96 hours (figure 1). According to these results,
our patient was diagnosed with delayed reaction to
aminopenicillin; and the recommendation was to
avoid penicillin altogether.

Discussion
DRESS syndrome is a potentially life-threatening
condition. It is a non-IgE mediated hypersensitivity
reaction to a drug that includes severe eruption of the
skin, fever, hematologic abnormalities (eosinophilia,
atypical lymphocytosis), lymphadenopathy, and the
involvement of internal organs (liver, kidney, lung).4
Its estimated incidence ranges from 1 in 1000 to 1
in 10 000 exposures to drugs.5 Although there have
been some reports of cases in children,6 most cases
occur in adults.

The pathogenesis of DRESS syndrome includes
drug-specific immune response and the reactivation
of herpesvirus infection, up to the point that the
detection of HHV-6 reactivation has been recent-
ly proposed as a diagnostic maker.7 In our patient,
both mechanisms were shown; the specific immune
response to amoxicillin (shown by the positivity of
delayed reading of IDT and patch test), and the reac-
tivation of HHV-6 infection (shown by the positivity
of pharyngeal culture to HHV-6). In spite of these
facts, our case did not completely meet the diagnos-
tic criteria of definitive DRESS syndrome according
to the Registry of Severe Cutaneous Adverse Reac-
tions (RegiSCAR) score,8 so a diagnosis of delayed
reaction to aminopenicillin was made.

In most patients, the reaction is characterized
by a long latency between the intake of the offending
medication and the onset of the disease (2 to 6
weeks),1 however, earlier outbreaks can occur, espe-
cially in previously sensitized patients. Our patient
had an atypical outbreak; the symptoms initiated just
one day after receiving amoxicillin, making the di-
gnosis more challenging. Despite its common uses,
amoxicillin without clavulanic acid has been seldom
reported as the primary instigator. Nevertheless, it
has mainly been involved as a cause of relapse of
DRESS syndrome since this drug often acts as an
aggravating factor due to the direct effect on her-
pesvirus replication.9 Thus, in patients with suspect-
ed DRESS syndrome, shortly after the initiation of
amoxicillin, it is important to search for other possi-
able drugs that have been recently introduced within
the last few weeks. In our case, amoxicillin was the
only causative drug since no other drugs had been
introduced in the previous months.

The diagnosis of delayed aminopenicillin re-
actions and DRESS syndrome is difficult; because
the pattern of the skin involvement and the types
of affected organs are diverse. Multiple diagnostic
criteria for DRESS syndrome have been proposed

Figure 1. Patch test (vaseline). Presence of wheal and
erthema indicating a positive reaction to amoxicillin 10%
(number 1), ampicillin 10% (number 2), cefuroxime 20%
(number 3), amoxicillin-clavulanic acid 10% (number 4),
but negative to cefuroxime 10% (number 5) at 96 hours.
in order to standardize the diagnosis. The European RegiSCAR has devised a scoring system based on: clinical features, the extent of the skin involvement, organ involvement, and clinical course. According to the final score, it rates DRESS cases as “no”, “possible”, “probable” or “definite” cases. In addition, other authors include HHV-6 activation in the diagnostic criteria.\(^7\)

The skin eruption and visceral involvement is usually resolved after drug cessation in an average time of six to nine weeks,\(^3\) although there have been reports of persistence or aggravation of the symptoms despite the discontinuation of the causative drug.\(^7\) A prompt withdrawal of the offending drug is the mainstay of the treatment of both delayed aminopenicillin reaction and DRESS syndrome. Patients without severe involvement can be treated symptomatically. For severe cases, systemic corticosteroids are commonly used.\(^3\) In our case, the use of corticosteroids was not necessary since the patient showed an early recovery with supportive measures only.

**Conclusions**

Our findings are compatible with a delayed aminopenicillin reaction associated to HHV-6 infection mimicking DRESS syndrome present with a very short latency period. Given the high variability of the clinical presentation, which began just one day after the causative drug had been initiated, the diagnosis of DRESS syndrome is improbable. In the other hand, an immune mechanism and a viral reactivation were shown; which is why the prompt withdrawal of the offending medication was an appropriate measure. Clinicians should not underestimate the potential complications of amoxicillin and they should be aware of this potentially life-threatening condition of this commonly prescribed drug in both adults and children in order to avoid delay in management and diagnosis.

**References**