Case Report

Severe Amoxicillin-Induced Rash and EBV reactivation: DRESS or VRESS?

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Abstract

Background: Amoxicillin-induced rash in mononucleosis syndrome is well known but its pathophysiology is discussed. In some cases amoxicillin-induced rash in infectious mononucleosis or in severe Epstein-Barr (EBV) virus reactivation may fulfil the diagnostic criteria of DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) without any other offending drug.

Objective: We propose the new acronym VRESS for Virus Reactivation with Eosinophilia and Systemic Symptoms corresponding to some severe virus reactions.

Study design: Case report and in vitro study

Results: A typical case of VRESS in a 87-year-old woman with a severe EBV reactivation is reported. We demonstrated that amoxicillin increased in vitro the replication of EBV in Raji cell line.

Discussion: We discuss the possible non-immunological mechanism of amoxicillin-induced reaction and demonstrate that amoxicillin may increase in vitro the replication. Severe amoxicillin-induced rash in infectious mononucleosis or in EBV reactivation may be closed to DRESS and fulfil the diagnostic criteria of DRESS [3,4].

BACKGROUND

Amoxicillin-induced rash in patients with infectious mononucleosis is well established [1]. However, its pathophysiology remains discussed. The interaction between amoxicillin and the virus is not clearly understood. We recently reported that amoxicillin intake at the beginning of a DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) associated to other drugs may induce a flare of this syndrome [2]. We proposed and demonstrated in vitro that amoxicillin may have a direct effect on HHV6 replication: amoxicillin increased the replication of HHV6. Severe amoxicillin-induced rash in infectious mononucleosis or in EBV reactivation may be closed to DRESS and fulfil the diagnostic criteria of DRESS [3,4].

OBJECTIVES

We reported a typical case of severe amoxicillin-induced rash and studied the effect of amoxicillin in three EBV cell lines on EBV replication. We proposed a new acronym VRESS for Virus Reactivation with Eosinophilia and Systemic Symptoms to denominate these severe Herpesvirus reactivation.

STUDY DESIGN

Case report

An 87-year-old woman was hospitalized for erythroderma with renal failure and pneumonia.

Her previous morbidities included hypertension, diabetes mellitus, and osteoporosis. She had already been hospitalized for a rhabdomyolysis without renal failure two weeks before for a few days. She lived alone in her house, fell down on the floor and was not able to stand up. She was brought to our emergency department and was successfully treated for a rhabdomyolysis. She was also treated for cystitis with ofloxacin, then 8 days later she received amoxicillin-clavulanic acid for a non-severe pneumonia. She was sent to a nursing home for seniors.

Two days later she complained of a maculopapular rash that rapidly evolved over the next day to erythroderma. She was admitted for rapid deterioration. She concomitantly developed fever, renal failure, and severe hypoxemia. Blood tests demonstrated eosinophilia [0.82 10⁹/mL] that was preceded by a short-time lymphopenia and monocytosis at admission. Liver
tests were normal. There was neither pulmonary embolism, nor cardiac insufficiency. Amoxicillin-clavulanic acid was stopped and spiramycin was debuted. Her regular treatment included telmisartan, lercanidipine, metformine, and bromazepam. She was not taking any known DRESS-associated drug, including strontium ranelate. She did not have any history of drug allergy. Bacteriological tests were negative. Viral tests demonstrated a severe EBV (Epstein-Barr Virus) reactivation with 660400 copies/mL. Serological tests ruled out a primary infection with positive anti-EBNA and anti-VCA IgG antibodies and absence of detection of anti-VCA IgM. Twelve days later EBV PCR was 120000 copies/mL.

The course was favourable after three weeks with normalization of renal and lung functions.

A diagnosis of severe amoxicillin-induced rash in EBV reactivation was made.

**In vitro study**

EBV replication in presence of amoxicillin was studied in three cell lines [5]. 10⁴ cells per mL of Raji cell line (50 copies of episomal EBV per cell, no viral production) were incubated during 24 hours in 24-well microtiter plates containing culture medium with two concentrations of amoxicillin (68 and 137 microM) or without amoxicillin as control. The EBV DNA was quantified by real-time PCR [6]. For each condition, experiments were performed 3 times.

Same studies were done with two other cell lines: P3HR1 (production of virus) and Namalwa (integrated EBV genome without viral production). Results were given in percentage as compared to the control.

In presence of amoxicillin an increase of EBV replication after 24 hours was observed only in Raji cells (Figure 1).

**DISCUSSION**

Amoxicillin is known to provoke exanthema in patients with EBV-induced infectious mononucleosis [7]. Amoxicillin is known to behave as a good hapten. The patient would have been previously sensitized to amoxicillin. The administration of amoxicillin would also be a new challenge. But this patient had no history of drug allergy.

We may speculate that amoxicillin acts as a booster of EBV reactivation. The current explanation of amoxicillin-induced rash in EBV is immunological. The viral infection would decrease the threshold of T cells reaction against the drug. But in many cases a new challenge with amoxicillin a long time after the viral infection does not induce a rash and in addition skin tests are often negative. A non allergic phenomenon may be proposed. We previously demonstrated that amoxicillin increases in vitro HHV-6 replication [2]. We demonstrated in this report the same action of amoxicillin on EBV replication in a lymphocyte B-cell line, namely Raji. This effect of amoxicillin on EBV replication was not observed in two other cell lines. It is probable that the virus needs to be in a special state to respond to amoxicillin. The mechanism of interaction between amoxicillin and EBV is not known. The drug could act on the epigenetic control of the viral infection. This in vitro interaction between EBV and amoxicillin was also demonstrated in vivo in a Japanese patient with ampicillin [1]. Saito-Katsuragi and coll. reported the case of a 23-year-old woman who developed an ampicillin-induced rash associated with EBV reactivation [1]. They monitored EBV DNA by PCR in peripheral mononuclear cells after iterative reintroduction of ampicillin. A high level of EBV-DNA was demonstrated 24 to 48 hours after every challenge with ampicillin before the development of a new rash at day 39, 90, and 165. This EBV reactivation decreased with time suggesting that the virus needed to be in a previous state of activation to react to amoxicillin. This may explain why the majority of the population does not react to amoxicillin in absence of EBV active infection.

With the working hypothesis of DRESS our patient could fulfill the Kardouni's criteria with a score of 5 (probable case): fever > or = 38.5°C: 0, erythroderma: 1, eosinophils: 1, renal failure: 1, lung involvement: 1, resolution > or = 15 days: 0 [3]. But no culprit drug was found. The manifestations began 10 and 2 days after introduction of ofloxacine and amoxicillin-davulanic acid, respectively. She did not have previous drug allergy. Ofloxacine is not classically associated with DRESS and the delay was short [7]. We suspected an amoxicillin induced rash in a patient with EBV reactivation.

The dermatologists learned with DRESS, the clinical and biological manifestations associated with herpesvirus reactivation. DRESS is considered as a systemic reaction to herpesvirus reactivation induced by some drugs [8,9]. The diagnosis of DRESS is now often discussed in front of maculopapular rash with eosinophilia and systemic symptoms in immunosuppressed patients. Erroneous diagnosis may be done [10,11]. One of the principal differential diagnoses of DRESS is a severe Herpesvirus reactivation. We propose the new acronym VRESS (Virus Reactivation with Eosinophilia and Systemic Symptoms) to define this picture. Figure 2A illustrates the differences between DRESS and VRESS. Reactivation of Herpesvirus in DRESS is due to an offending drug (such as allopurinol, anticonvulsant, minocycline, sulfasalazine.). The long period of 2 to 6 weeks between the first drug intake and the development of DRESS is necessary for the reactivation of Herpes viruses. In DRESS the viral reactivation is the consequence of the drug intake. In VRESS we cannot find a classical culprit drug associated with DRESS. Herpesvirus reactivation is not induced...
A) Infectious mononucleosis with minime rash

EBV

Amoxicillin

Rash

B) Immunosuppression (transplant recipient, intensive care unit, stress)

Exanthema

VRESS

EBV or/and other HHV

Visceral manifestations

C) VRESS

EBV or/and other HHV

Rash

VRESS with amoxicillin-induced flare

Figure 2 Schematic representations of DRESS and VRESS (Figure 2A). Amoxicillin-induced rash is illustrated in EBV infection (Figure 2B), and in VRESS (Figure 2C).

by a drug but may be a consequence of immunosuppression or a severe condition. In both conditions amoxicillin may act as a booster of an ongoing EBV (or other herpesviruses) reactivation (Figure 2B-2C). In VRESS the delay between amoxicillin intake and development or flare of the rash is short (24 to 48 hours).

VRESS is often observed in immunosuppressed patients or in patients who are hospitalized in intensive care units. We recently published a demonstrative case of VRESS in a HIV-infected patient as a manifestation of immune reconstitution inflammatory syndrome [12]. VRESS are very more frequent than DRESS. Dermatologists are frequently asked for the diagnosis of DRESS in intensive care units. In many cases these patients do not develop DRESS but VRESS because reactivations of Herpesviruses (HSV, CMV, EBV, HHV-6, HHV-7, VZV) are very common in case of immunosuppression or stressful conditions. Moreover administration of amoxicillin is very usual and may also participate in the increase of replication of Herpesviruses.

This case illustrates a VRESS syndrome. It is possible that the first episode with rhabdomyolysis induced EBV reactivation in this old woman. We suspected that EBV reactivation in association with amoxicillin intake induced a severe maculopapular rash with systemic symptoms. At admission a lymphopenia with monocytosis was observed. It was not possible to elucidate whether the monocytosis was a mononucleosis syndrome. The result was given by an automated machine without blood smear examination.

Although eosinophilia is frequently observed in hypersensitivity drug reaction, this criteria does not rule out a viral infection. Eosinophilia may be observed in severe viral infection [13]. Eosinophilia is often preceded (as in DRESS) by lymphopenia, and mononucleosis syndrome or lymphocytosis. In feline herpes virus infection, eosinophilia and eosinophilic dermatitis is frequent [14].

We suggest that in absence of previous amoxicillin allergy the development of rash with eosinophilia (or lymphopenia/lymphocytosis/mononucleosis syndrome) and systemic manifestations shortly after amoxicillin intake may be a marker of Herpesvirus active infection (primary infection or reactivation). Physician must look for EBV, CMV, HHV-6, and HHV-7 reactivation. Real time quantitative PCR are the most reliable tests. The difference between VRESS and DRESS is important to know because some drugs may be considered to be responsible for manifestations when these systemic manifestations are only the consequence of Herpesvirus reactivations. VRESS may also require specific antiviral treatment.

REFERENCES


Cite this article