

### Drug-induced aseptic meningitis: A possible T-cell-mediated hypersensitivity

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#### Clinical Implications

- Amoxicillin-induced T-cell activation has been detected in 2 patients suffering from drug-induced aseptic meningitis (DIAM), suggesting a delayed hypersensitivity mechanism. Lymphocyte transformation tests or enzyme-linked immunosorbent spot assays performed on the peripheral blood or cerebrospinal fluid could be useful tools to explore the pathogenesis of DIAM.

#### TO THE EDITOR:

Drug-induced aseptic meningitis (DIAM) is an inflammatory reaction of the brain membranes due to a drug agent. The most frequent culprit drugs are nonsteroidal anti-inflammatory drugs, antimicrobials, intravenous immunoglobulins, intrathecal agents, and vaccines.<sup>1</sup> Using *in vitro* assays, we detected an amoxicillin-induced T-cell activation in 2 patients suffering from DIAM, suggesting a delayed hypersensitivity mechanism.

Patient 1, a 62-year-old woman without chronic medical conditions, was admitted to hospital for severe headaches and fever, which started a few hours after amoxicillin intake. A careful review of her medical history revealed 3 previous similar episodes in the past 6 years (Table 1). Skin test results (patch tests and immediate and delayed intradermal tests) were negative with amoxicillin, ceftriaxone, and cefpodoxim (used as controls). The patient experienced mild headaches 24 hours after a single oral challenge with 500 mg amoxicillin. To investigate the presence of circulating amoxicillin-specific T cells, IFN- $\gamma$  and granzyme B (GrB) enzyme-linked immunosorbent spot (ELISPOT) assays were performed on the patient's PBMCs, as described previously.<sup>2</sup> A high frequency of IFN- $\gamma$  and GrB drug-induced secreting cells was shown only with amoxicillin restimulation, but not with an irrelevant drug (ceftriaxone) (Figure 1, A).

Patient 2 was a 32-year-old woman without a significant medical history. She reported 3 previous episodes of meningitis after amoxicillin intake (Table 1). The symptoms spontaneously stopped after treatment discontinuation. Cerebrospinal fluid (CSF) examination showed aseptic meningitis during the first episode. Patch test and intradermal test results with amoxicillin

were negative. Lymphocyte transformation test (LTT) result with amoxicillin was positive (stimulation index >2), whereas LTT result with ceftriaxone was negative (Figure 1, B).

For these 2 patients, bacterial, viral, and autoimmune causes of meningitis were carefully ruled out. Finally, the diagnosis of amoxicillin-related aseptic meningitis was retained by the Pharmacovigilance Department as a definite adverse drug reaction according to the Naranjo Adverse Drug Reactions Probability Scale, with a score of 9 or more.<sup>3</sup> Amoxicillin was advised as being contraindicated and the patients did not experience meningitis relapse. Drug challenges with ceftriaxone and cefpodoxim were well tolerated, allowing the use of these molecules as alternative treatment.

The immunopathological mechanism and the nature of cells involved in DIAM remain yet to be fully understood. A type III hypersensitivity reaction was first hypothesized, supported by the finding of specific drug-IgG complex in CSF or blood.<sup>1</sup> However, Kastenbauer et al<sup>4</sup> found no evidence of type I or III reaction, with no detection of specific IgE or circulating immune complexes.<sup>4</sup> More recently, a T-cell-mediated delayed hypersensitivity has been suspected, according to the time course of DIAM, the cellular changes in CSF, and a positive LTT result in a patient with a vitamin B complex-induced meningitis.<sup>5</sup>

Patch test is one of the most reliable *in vivo* tools to explore T-cell delayed hypersensitivity to amoxicillin, but the relevance of skin tests in aseptic meningitis is doubtful as illustrated here. This could be due to a particular phenotype of T cell involved in DIAM with a meningeal tropism and an inflammatory response restricted to the meningeal tissue. In this context, *in vitro* functional tests might be alternative useful tools. ELISPOT assay is used to quantify the secretion/activation of drug-specific cells, in the field of drug-induced hypersensitivity. In our first patient, the ELISPOT assay evidenced drug-specific cells producing high amount of IFN- $\gamma$  and GrB. IFN- $\gamma$  is a key T<sub>H</sub>1-type cytokine released from activated T cells in drug-induced delayed hypersensitivity.<sup>6</sup> Interestingly, IFN- $\gamma$  increase in CSF is also detected in patients with nonviral aseptic meningitis, which may suggest a T-cell accumulation in the central nervous system.<sup>7</sup> GrB is a serine protease released from cytoplasmic granules within cytotoxic T cells and natural killer cells acting as a key mediator of targeted cell death. Previous studies have suggested the involvement of cytotoxic cells in various drug-induced cutaneous diseases and the value of the ELISPOT assay to detect GrB-secreting cells in the peripheral blood of these patients.<sup>8</sup> LTT is used for the *in vitro* evaluation of T-cell-mediated cutaneous hypersensitivity.<sup>9</sup> It highlights the presence of circulating drug-specific T cells. Taken together, our results suggest that DIAM could be a cytotoxic T-cell-mediated delayed hypersensitivity. We think that LTT and ELISPOT assays performed on the peripheral blood or CSF are interesting tools to explore the pathogenesis not only of DIAM but also of other suspected immunoallergic reactions when performed in the peripheral blood. They might be an asset to identify the culprit drug, improving the prompt recognition of these diseases and avoiding harmful rechallenge with the offending drug.

TABLE 1. Characteristics of patients' reactions

| Characteristic                              | Patient 1                                                                                             |                                      |                                                                                     |                                                                                     | Patient 2                                                                      |                                                               |                                                |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------|
| Reaction no.                                | First                                                                                                 | Second                               | Third                                                                               | Fourth                                                                              | First                                                                          | Second                                                        | Third                                          |
| Initial disorder                            | Sinusitis                                                                                             | <i>Helicobacter pylori</i> infection | Rhinorrhea, fever                                                                   | Dental troubles                                                                     | Dental troubles                                                                | Dog bite                                                      | Rechallenge                                    |
| Antibiotic                                  | Amoxicillin/clavulanic acid                                                                           | Amoxicillin and clarythromycin       | Amoxicillin                                                                         | Amoxicillin                                                                         | Amoxicillin/clavulanic acid and metronidazol                                   | Amoxicillin                                                   | Amoxicillin                                    |
| Symptom onset after first drug intake (day) | 7                                                                                                     | 3                                    | 3                                                                                   | 0.5                                                                                 | 0.5                                                                            | 0.25                                                          | 0.1                                            |
| Symptoms                                    | Fever, headaches                                                                                      | Fever, headaches, nausea, vomiting   | Fever, headaches                                                                    | Fever, headaches, vomiting,                                                         | Headache, neck stiffness, photophobia, asthenia, nausea                        | Headache, neck stiffness, photophobia, asthenia, facial edema | Headache, neck stiffness, photophobia, myalgia |
| CSF examination                             | Lymphocytic pleocytosis<br>High protein level<br>Normal glucose<br>No organism                        | ND                                   | Lymphocytic pleocytosis<br>Subnormal protein level<br>Normal glucose<br>No organism | Lymphocytic pleocytosis<br>Subnormal protein level<br>Normal glucose<br>No organism | Lymphocytic pleocytosis<br>High protein level<br>Normal glucose<br>No organism | ND                                                            | ND                                             |
| Other investigations                        | Blood cultures: negative<br>Enterovirus and herpes virus PCR: negative<br>Normal EEG and cerebral MRI | ND                                   | Normal cerebral MRI<br>EBV, CMV, and herpes virus PCR: negative                     | Herpes virus PCR: negative                                                          | Normal cerebral CT scan                                                        | ND                                                            | ND                                             |

CMV, Cytomegalovirus; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; ND, not done.

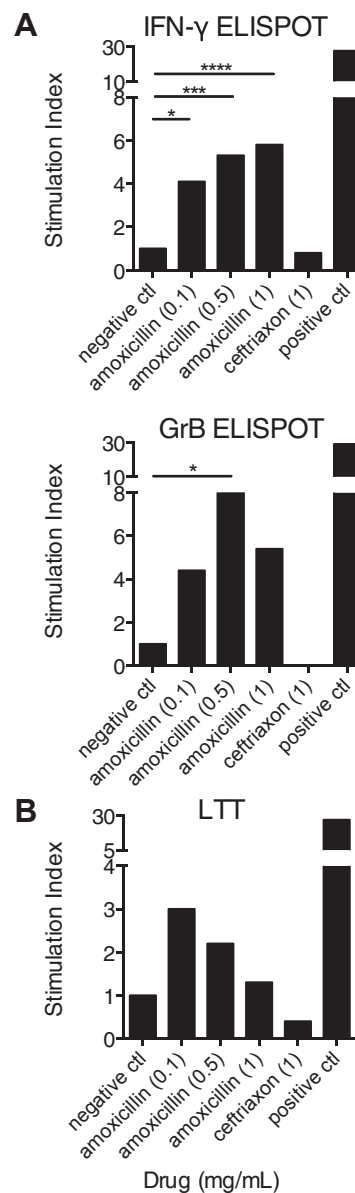


**FIGURE 1.** Amoxicillin-induced T-cell response in 2 DIAM cases. IFN-γ ELISPOT, GrB ELISPOT, and LTT were performed in the absence or presence of amoxicillin with 3 concentrations, ceftriaxone (irrelevant drug), or anti-CD3 (OKT3 1 μg/mL, positive control). ELISPOT and LTT were, respectively, incubated 24 hours and 5 days. **A**, Patient 1 with positive IFN-γ and GrB ELISPOTs after amoxicillin restimulation. Results are expressed in number of IFN-γ and GrB SFCs/10<sup>6</sup> PBMCs. A positive test result was defined by a stimulation index of more than 3. Error bars represent the mean ± SEM. \*  $P \leq .05$ , \*\*\* $P \leq .001$ , \*\*\*\* $P \leq .0001$ . **B**, Patient 2 with a positive LTT result with amoxicillin. Results are expressed in stimulation index, which was interpreted as positive when more than 2.0. *Ctrl*, Control; *SFCs*, spot-forming cells.

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