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CASE REPORT

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Drug-Induced Enterocolitis Syndrome with Amoxicillin-Clavulanic Acid and Alternative Beta Lactam Antibiotic

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ABSTRACT

Drug-induced enterocolitis syndrome (DIES) is a rare hypersensitivity reaction characterized by delayed gastrointestinal symptoms following ingestion of triggering medications. We report the case of a seven-year-old male presenting with symptoms consistent with DIES after receiving amoxicillin-clavulanic acid (AMX/CLV) for tonsillitis and soft tissue infection.

The patient experienced recurrent vomiting and lethargy 2-3 hours post-administration of AMX/CLV. Following supportive care and clarithromycin treatment, the symptoms resolved. Oral provocation testing with AMX/CLV resulted in severe abdominal pain, vomiting, and lethargy, confirming DIES. Patch testing with various beta-lactam antibiotics yielded negative results. Subsequent oral provocation with cefuroxime axetil showed no adverse reactions, suggesting an alternative.

This case highlights the importance of considering DIES as a differential diagnosis in patients presenting with delayed gastrointestinal symptoms following drug intake. Identifying alternative antibiotics is crucial for the management of such cases.

Keywords: Pediatric, drug-induced enterocolitis syndrome, amoxicillin/clavulanic acid, alternative antibiotic

INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) was first described in detail at the end of the 20th century as a non-IgE-mediated food allergy characterized by delayed gastrointestinal symptoms following the ingestion of a trigger food. In 2014, Novembre et al. coined the term Drug-Induced Enterocolitis Syndrome (DIES) for the first time, based on the similarity of clinical findings and laboratory investigations to FPIES criteria in a six-year-old girl who developed prolonged vomiting, diarrhea, pallor, and lethargy two hours after oral Amoxicillin (AMX) intake (1).

We present our case of DIES, which is rarely reported in the literature, to emphasize that enterocolitis can occur not only with foods but also rarely with drugs, and to indicate a beta-lactam antibiotic.

CASE PRESENTATION

A seven-year-old male patient presented to the emergency department due to recurrent vomiting and lethargy after the first dose of amoxicillin-clavulanate (AMX/CLV) was administered at two different times for tonsillitis and soft tissue infection. Intravenous fluid support and antiemetic therapy improved the clinical symptoms. The

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treatment was switched to clarithromycin, and the patient completed the course successfully. Since the patient did not exhibit skin or respiratory findings suggestive of an IgE-mediated reaction, a diagnostic oral provocation test was planned without skin prick test and intradermal test.

The patient was scheduled to undergo an open drug provocation test (DPT) with informed consent from her family. The AMX/CLV syrup was divided into three doses, each representing 10-30-60% of the total therapeutic dose (reaching a total of 60 mg/kg/day), and administered at 30-minute intervals (2). Two and a half hours after the last dose, the patient developed severe abdominal pain, intermittent severe vomiting three times, lethargy, and pallor. On assessment of vital signs, oxygen saturation was 97%, respiratory rate was 20/min, blood pressure was 100/60 mmHg, and heart rate was 95/min. Due to the patient's recurrent vomiting and lethargy, a bolus of normal saline was administered at a rate of 20 ml/kg. Laboratory investigations revealed WBC: $12.98x10^9$/L, neutrophils: $9.15x10^9$/L, PLT: $401x10^9$/L, CRP: negative, urea: 30 mg/dL, and creatinine: 0,42 mg/dL; and blood electrolytes were within the normal physiological range. Abdominal pain improved and there was no recurrence of vomiting, but watery diarrhea developed during follow-up. On the day of the challenge test, there was no infectious context or other confounding factors.

Patch tests with penicillin V, AMX/CLV and cefuroxime axetil in petrolatum at concentrations of 10% and 20% were performed four weeks after the development of the reaction. No reaction was observed at 48 hours and at 72 hours after the patch test. DPT was performed with cefuroxime axetil for the identification of a alternative beta-lactam antibiotic for the patient. Cefuroxime axetil was administered by dose escalation. Doses equivalent to 10-30-60% of the therapeutic dose (30 mg/kg/day) were administered every 30 minutes (3). After the last dose, the patient was under clinical observation for 4 hours, during which time there was no development of a reaction.

DISCUSSION

DIES is a rare delayed (approximately 1-4 hours after ingestion), IgE-independent hypersensitivity reaction whose pathogenesis is not fully understood (3). Recent work focuses on the role of T cells in the immunopathogenesis. Studies have suggested that disruption of the intestinal barrier, changes in microbiota composition, and a dysregulated immune response may play roles in both FPIES and DIES. Reactive metabolites of the drug or drug-protein complexes are thought to cause the reaction by affecting the gastrointestinal epithelium through an immunological response (4). A T cell-mediated response or activation of innate immunity has been proposed for FPIES, and this may also occur in DIES. A recently published clinical letter reported T cell involvement in the pathogenesis of DIES (5). There is currently no validated biomarker diagnosis. Typical signs include recurrent delayed vomiting, diarrhea, and low blood pressure that may result in dehydration and hypovolemic shock. In 2017, diagnostic criteria for patients with suspected DIES were proposed, adapted from Nowak-Wegrzyn et al.'s International consensus guidelines for the diagnosis and management of FPIES (6). DIES shares with FPIES the clinical presentation of vomiting within 1 to 4 hours of the ingestion of the suspected drug and the absence of classic IgE-mediated allergic cutaneous or respiratory symptoms as key diagnostic criteria. Minor criteria were identified: a second episode of repetitive vomiting after ingestion of the same drug, repetitive vomiting episode 1–4 h after ingestion of a different drug , extreme lethargy , marked pallor, need for emergency department admission, need for intravenous fluid support , diarrhea 24 h (usually 5–10 h) after ingested drug, hypotension, and hypothermia. The diagnosis of DIES requires that a patient meet the major criteria and at least 3 minor criteria (1,7). Although there is currently no specific laboratory criterion for DIES, elevated levels of neutrophils, which indicate inflammation, are commonly observed. Thrombocytosis and slightly increased methemoglobinemia have also been reported in some cases. These findings deserve further study as potential diagnostic support parameters (8,9). Although not required for the diagnosis, a DPT is strongly recommended if a single episode occurred in order to properly confirm or exclude the diagnosis and to reduce the risk of overdiagnosis (4).

Unlike FPIES, DIES can also occur with previously tolerated medications. Because of the few identified cases, time of recovery from the disease is well established for FPIES but still unknown for DIES. Although there is no established treatment protocol for DIES, management is mainly supportive. Similar to FPIES, treatment consists mostly of saline solution infusion, ondansetron and corticosteroids (4).

A comprehensive review of the literature shows that, to date, 9 cases of DIES have been identified in children and 12 in adults. The responsible drug was found to be AMX and/or AMX/CLV in 10 cases, pantoprazole in one adult case, and paracetamol in one infant case (4,10,11). Further studies are needed to better understand whether this syndrome can also be caused by other drugs.

Our patient is presented as the 10th pediatric case of DIES in the literature to increase awareness of this rare but potentially serious clinical condition associated with potential complications. Our patient met the diagnostic criteria defined in the literature for DIES. Additionally, neutrophilia, which is thought to result from inflammation and is considered a common laboratory finding in DIES (though not a diagnostic criterion), was also observed in our patient. Another contribution of our case to the literature is demonstrating tolerability to cefuroxime axetil following the DPT. Data regarding cross-reactivity in the presence of DIES is quite rare in the literature. Tolerability of phenoxymethyl penicillin in children diagnosed with DIES associated with AMX suggested that the side chain of AMX and not the b-lactam ring side is responsible for allergy to penicillins (12-14). The negative DPT result with cefuroxime axetil in our case suggests that cephalosporins with no shared side chain with AMX can be tolerated. Supportively, in the literature, a 10-year-old patient diagnosed with DIES with AMX was shown to tolerate cefpodoxime (15). The delayed onset of symptoms in DIES, following drug intake, suggests a T-cell-mediated immune response rather than IgE-mediated mechanisms. Atopy patch tests are commonly utilized to diagnose non-immediate T-cell-mediated drug hypersensitivity reactions. In our case, a patch test with AMX was performed and found to be negative. There have been no reported cases in the literature of DIES with positive patch tests to the suspected drug. However, this may be associated with the limited diagnostic value of patch tests in drug allergies.

Thus, large multicenter studies are needed to assess the prevalence, pathophysiology, clinical course and cross-reactivity characteristics of this rarely described drug allergy.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Authorship Contributions

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