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CASE REPORT

Drug-induced chronic bullous disease of childhood in a two-year-old Filipino male triggered by cefaclor or cefuroxime: A case report

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ABSTRACT

INTRODUCTION Chronic bullous disease of childhood (CBDC) is a rare immune-mediated subepidermal vesiculobullous eruption, characterized by linear IgA deposition along the basement membrane zone of the skin. Although mostly idiopathic, CBDC may be triggered by factors such as infection, and drugs. Clinical and immunohistopathological features of drug-induced cases are heterogeneous and indistinguishable from the idiopathic form.

CASE REPORT A two-year-old Filipino male presented with pruritic vesicles and bullae on the back several days after finishing a course of cefuroxime, and cefaclor. Examination revealed multiple tense vesicles and bullae, some coalescing into a rosette pattern with central crusts on the perioral, scalp, neck, back, perineal, and perianal areas.

Histopathology showed a subepidermal split with neutrophilic and eosinophilic infiltrates. Direct immunofluorescence revealed strong linear deposition of IgA, and granular deposits of C3 and IgM at the basement membrane zone, thus confirming the diagnosis of CBDC.

Dapsone at 2mg/kg/day was started, with oral prednisolone (1.3mg/kg/day), and cloxacillin syrup (40mg/kg/day). Topical care with betamethasone dipropionate and mupirocin ointment was included. After eight weeks, patient showed significant improvement with few vesicles and resolved lesions healing with post-inflammatory hyperpigmentation.

CONCLUSION We report a case of a two-year-old male presenting with vesiculobullous lesions after a course of cefuroxime, and cefaclor. As both were given and withdrawn in a period of close proximity, it is difficult to determine the probable culprit drug. Spontaneous resolution upon withdrawal of the suspected drug is variable. Systemic therapy such as dapsone may be necessary for treatment.

KEYWORDS vesiculobullous, linear IgA bullous dermatosis, cefaclor, cefuroxime

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INTRODUCTION

Chronic bullous disease of childhood (CBDC) and linear IgA bullous dermatosis (LABD), are rare immune-mediated subepidermal vesiculobullous eruption with different presentations of the same disease process.[1]

International data of LABD shows incidence of 0.5 to 2.3 cases per million individuals per year.[2] Locally, data gathered from the Philippine Dermatological Society Health Information System (PDS HIS) show a total of 142 newly diagnosed cases of CBDC from 2011 to 2018.[3]

Most cases of CBDC are idiopathic, however, it may also be triggered by infection, drugs, vaccinations, and malignancy. However, it may also be triggered by infection, drugs, vaccinations, and malignancy.[4] Drug-induced cases are highly heterogeneous and completely indistinguishable from the idiopathic form, and are more commonly reported among adults as LABD.[5]

In this case report, we describe a case of CBDC in a two-year-old Filipino male who presented with vesicles and bullae after finishing a course of cefuroxime, and cefaclor.

CASE REPORT

A two-year-old Filipino male presented with pruritic vesicles, and bullae on the perioral, scalp, neck, back, perineal, and perianal areas of eight days' duration. Three weeks prior to consultation, the patient was admitted for sepsis from unspecified organism. Cefuroxime was given for five days and was shifted thereafter to cefaclor for seven days with complete recovery.

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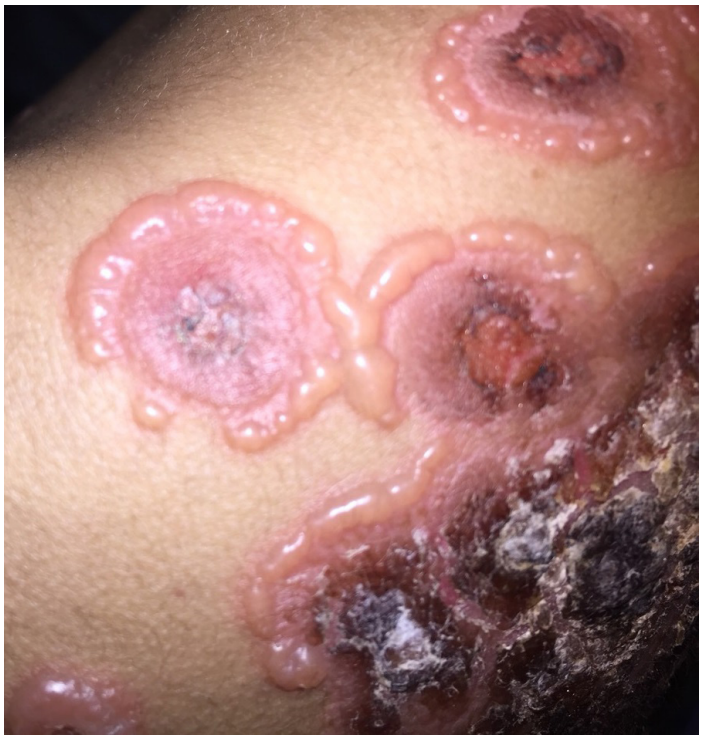

Figure 1. Vesicles and bullae coalescing into a rosette pattern with central crusts.

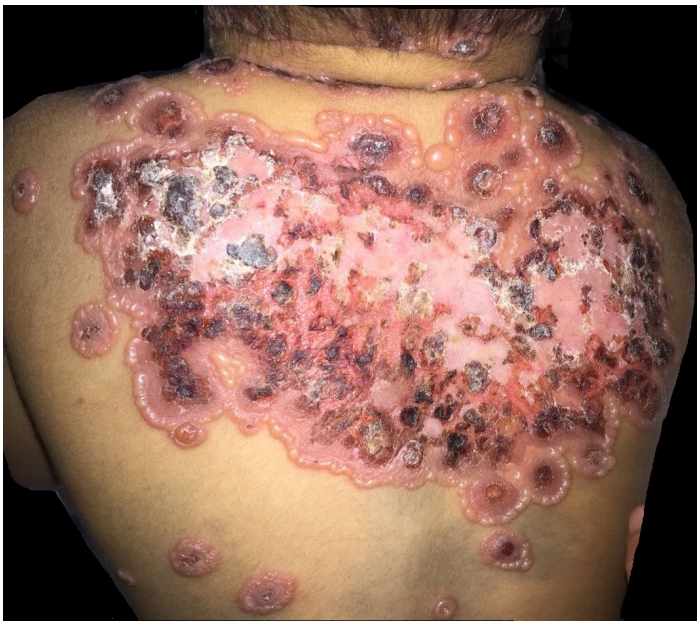

Figure 2. Tense vesicles and bullae with areas of moist erosion and brown crusts on the upper back.

A few days after completing the antibiotics treatment, multiple pruritic vesicles with an erythematous base appeared on the upper back. He was started on a five-day course of acyclovir, which he completed. However, new vesicles continued to present prompting consult, and admission.

Past medical history showed a positive skin test to ceftriaxone, others were unremarkable. Examination showed multiple tense vesicles, and bullae on an erythematous base, coalescing in a rosette pattern (Figure 1), with areas of moist erosion and brown crusts on the perioral, scalp, neck, back, perineal, and perianal areas (Figure 2).

Laboratory evaluation revealed leukocytosis with a WBC count of 18,380 mm^3 (RI: 4,800-10,800 mm^3). Gram stain revealed gram positive cocci in pairs and small clusters. Histopathologic findings showed subepidermal vesiculobullous disease consistent with CBDC, with neutrophilic and eosinophilic infiltrates in the blister cavity (Figure 3). Direct immunofluorescence showed a strong linear IgA deposit, and weak granular deposit of C3 and IgM along the basement membrane zone (Figure 4). Based on the clinicopathologic features, the diagnosis of CBDC was made.

The patient was started on oxacillin (165mg/kg/day), and hydrocortisone (4mg/kg/day), along with betamethasone dipropionate, and mupirocin ointment. Hydrocortisone was shifted to oral prednisolone (1.3mg/kg/day), which was continued upon discharge. Antibiotic was shifted to oral cloxacillin (40mg/kg/day), and topical care was continued daily. The patient was also started on dapsone at 2mg/kg/day.

After five weeks of dapsone and prednisolone, the patient's mother noted a decrease in the number and size of new blisters. At eight weeks of treatment, there was significant improvement wherein fewer blisters were present, and previous lesions healed with post-inflammatory hyperpigmentation.

During the course of treatment, laboratory evaluation was done regularly. At eight weeks of dapsone, complete blood count showed decreased hemoglobin (11.2 g/dL RI: 13-17 g/dL), hematocrit (35.8% RI: 40-52%), and red blood cell count (4.58 mil/mm^3 RI: 4.7-6.1 mil/mm^3), with corresponding reticulocytosis (2.5% RI: 0.5-2%) which is expected with dapsone intake. Improvement of counts was eventually observed at eleven weeks of treatment.

No untoward adverse events were noted. However, the patient was then lost to follow-up. The mother self-medicated, and tapered administration of dapsone (2mg/kg/day) to twice or thrice a week, and discontinued oral prednisolone, cloxacillin, and topical care. Recurrence after four months was noted with increase in vesicles prompting follow-up, hence the patient was restarted on dapsone (2mg/kg/day), prednisolone (1.3mg/kg/day), cloxacillin (30mg/kg/day), and daily topical care.

As of time of this writing, the patient is still undergoing treatment with plans to taper accordingly and to continue regular monitoring for adverse events.

DISCUSSION

Drug-induced LABD in adults can occur in 37.5% of cases, while

CBDC induced by drug is less common in the pediatric population.[6] Drugs involved may elicit an autoimmune response, where they may act as haptens, causing a break in the self-tolerance of native antigens. Possible antigens to the disease are two proteins (97-kD and 285-kD) found in both the lamina lucida and sublamina densa. Moreover, drug-specific T cells and cytokines increase IgA antibody synthesis that deposit along the basement membrane zone in CBDC.[7] Studies have also suggested that infection may serve as the triggering or aggravating event, as this serves as cofactors of the immunologic response of drug-induced LABD or CBDC.[8] The drug-induced variant is difficult to distinguish from the idiopathic subtype, as in both cases, autoantibodies are directed to the same heterogeneous group of proteins.[9]

Vancomycin is the most common drug involved in drug-induced LABD, followed by phenytoin and trimethoprim/sulfamethoxazole.[5,9] In contrast to pencillin-derived medications reported to induce LABD, ixoxazolyl penicillins such as oxacillin and cloxacillin which were used in the case have been reported as effective treatment options for LABD.[2] There are limited published case reports on drug-induced LABD secondary to cephalosporins, much less drug-induced CBDC. While there is one published report of drug-induced LABD due to cefuroxime,[8] no such report has been made implicating cefaclor among adults. More specifically, and to the best of our knowledge, there are no published cases of drug-induced CBDC secondary to either cefaclor or cefuroxime. In the case presented, either cefuroxime or cefaclor may be the culprit drug as both were administered and withdrawn in close proximity.[5]

Currently, the typical features of a drug-induced subtype are yet to be elucidated. Nonetheless, the most important characteristic of a drug-induced CBDC is the temporal sequence of drug administration and onset of symptoms.[9] Algorithms have been developed to strengthen causality between the suspected drug and the adverse event such as the Naranjo score.[9,10] Using this algorithm, the patient was able to garner two points that fall under the probability score of "possible adverse drug reaction," namely there had been previous reports of the reaction in the drug, specifically cefuroxime[8] (one point), and event appeared after the suspected drug was given (two points). Since the patient had an infection that might have triggered the disease, a point is deducted from the score, giving us the total of two points.

Challenge-dechallenge-rechallenge protocol remains to be the gold standard for confirming the diagnosis of a drug-induced event.[9] Such rechallenge may result to severe recurrence and longer disease course, hence only a few cases have been confirmed by this procedure.[5,9] For ethical reasons, rechallenge was not done in the patient.

Idiopathic CBDC is usually self-limiting and remits in months or years.[2] First line of treatment include dapsone supplemented with medications such as corticosteroids and antibiotics.[7] Though the optimal therapeutic option in drug-induced CBDC is the discontinuation of the suspected drug, less than 50% of cases have spontaneous resolution upon

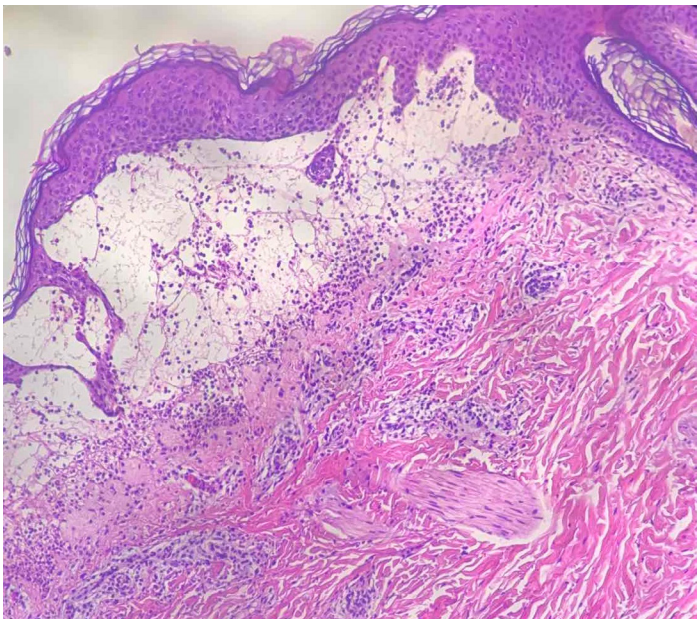

Figure 3. Subepidermal split with neutrophilic and eosinophilic infiltrates in the blister cavity.

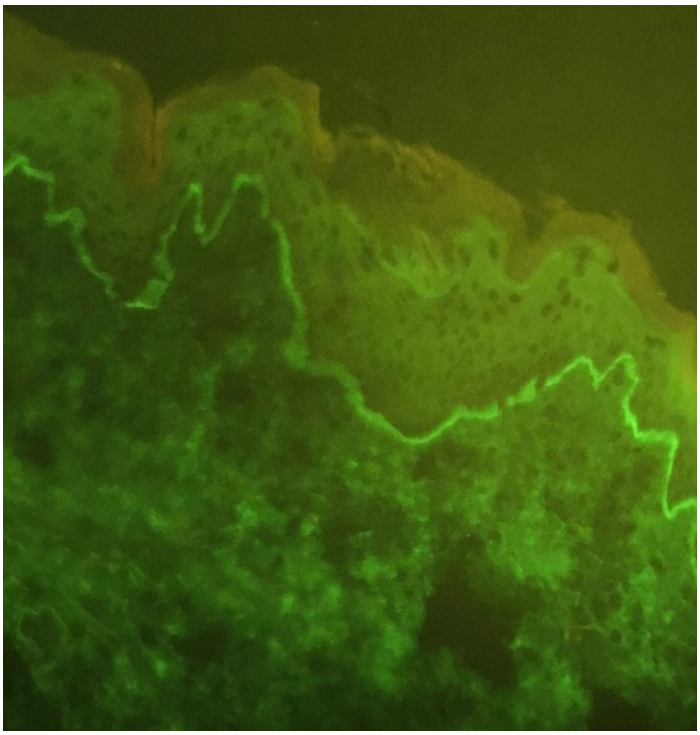

Figure 4. Strong linear IgA deposit (+2) along the basement membrane zone.

withdrawal.[5] Additional therapy for drug-induced cases may be needed to avoid the amplification of the disease, resulting in a self-maintaining immune response.[5,9] In the case presented, gradual remission was observed eight weeks into treatment with dapsone, prednisolone, cloxacillin, topical betamethasone dipropionate, and mupirocin ointment.

CONCLUSION

We report a case of a two-year-old male presenting with vesicles, and bullae several days after finishing a course of cefuroxime, and cefaclor for sepsis. As both drugs were given, and withdrawn in a period of close proximity from each other and to the onset of symptoms, it is difficult to determine the definite culprit drug that caused the drug-induced CBDC. Gradual response was noted with dapsone and prednisolone. In contrast to idiopathic CBDC which is a self-limited disease, spontaneous resolution upon withdrawal of the suspected drug in drug-induced cases is variable. Systemic therapy such as dapsone may be necessary for treatment.

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