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CASE REPORT

# Development of Bullous Acrodermatitis Enteropathica during the Course of Chemotherapy for Acute Lymphocytic Leukemia

Ji Hoon Chun, M.D., Ji Hye Baek, M.D., Nak Gyun Chung, M.D.[1], Jung Eun Kim, M.D., Baik Kee Cho, M.D., Hyun Jeong Park, M.D.

*Departments of Dermatology and [1]Pediatrics, St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea*

Acrodermatitis enteropathica (AE) is an uncommon autosomal recessive genetic disorder of zinc malabsorption. The acquired form may be associated with inadequate intake, impaired absorption, and increased excretion of zinc. Those afflicted present with diarrhea, stomatitis, psychiatric symptoms, non-scarring alopecia, and nail dystrophy accompanied by erythematous which appears as scaly patches with erosion vesicles and pustules mostly affecting the extremities, perineal, and periorificial areas. Due to the variable findings of most case reports, the clinical and histopathological features of AE are often regarded as non-specific. We report an unusual case of bullous AE secondary to total parenteral nutrition for the treatment of acute pancreatitis occurring in a six-year-old male with acute lymphocytic leukemia who underwent chemotherapy. He presented with periorificial, reddish, eroded bullae with multiple vesicles and blisters on his fingers, toes, and buttock, showing necrotic keratinocytes with multiple intraepidermal vesicles and perivascular infiltration with predominant lymphocytes and few neutrophils within the dermis. To the best of our knowledge, this is the first case report of bullous AE in the Korean dermatologic literature. **(Ann Dermatol 23(S3) S326~S328, 2011)**

**-Keywords-**
Bullous acrodermatitis enteropathica, Chemotherapy, Total parenteral nutrition

## INTRODUCTION

Acrodermatitis enteropathica (AE) is a rare hereditary or acquired disorder of zinc deficiency first described in 1942[1]. The condition is characterized by alopecia, diarrhea, lethargy, acute eczematous and erosive acro-orificial dermatitis, and acute paronychia[2]. A rare variant of AE, bullous AE, has unique histopathological findings encompassing clustered and individual necrotic keratinocytes, intraepidermal vesiculation with scant spongiosis, and a mostly lymphoneutrophilic infiltration within the vesicles[3]. We experienced a case of bullous AE secondary to total parenteral nutrition (TPN) for the treatment of acute pancreatitis occurring in a six-year-old male with acute lymphocytic leukemia who underwent chemotherapy. To our knowledge, this is the first report of bullous AE in the Korean dermatologic literature. Here, we report our case with a review of the associated literature.

## CASE REPORT

A six-year-old male was transferred to the Catholic Hematopoietic Stem Cell Transplantation Center in December, 2008 with acute pancreatitis, hypertension, and

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**Corresponding author:** Hyun Jeong Park, M.D., Department of Dermatology, St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 62 Yeouido-dong, Yeongdeungpo-gu, Seoul 150-713, Korea. Tel: 82-2-3779-1230, Fax: 82-2-783-7604, E-mail: hjpark@catholic.ac.kr

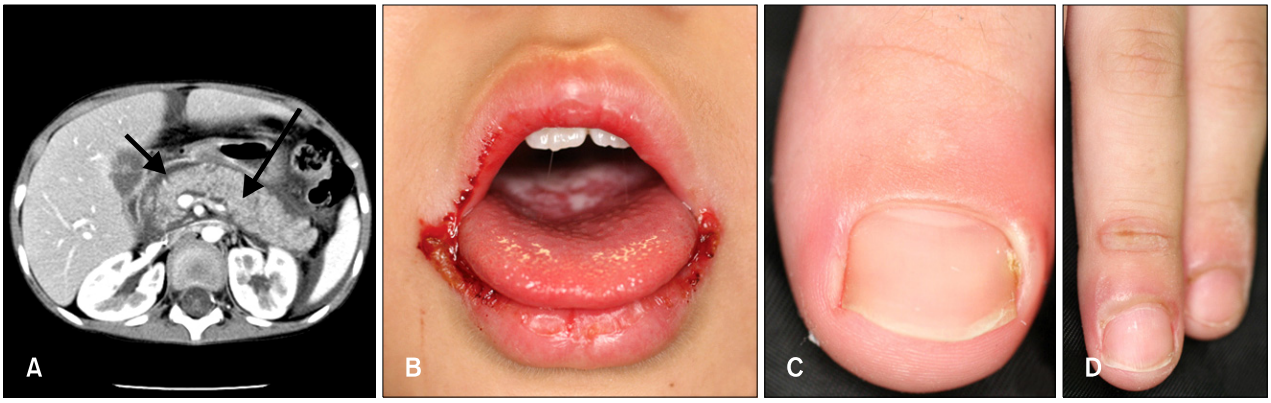


**Fig. 1.** (A) Abdominal computed tomography showing diffuse edematous swelling of the pancreas (long arrow) and extensive peripancreatic fluid collection (short arrow), (B) reddish, eroded vesicles involving periorificial area, (C) and (D) paronychia with vesicle and blister formation involving fingers and toes.

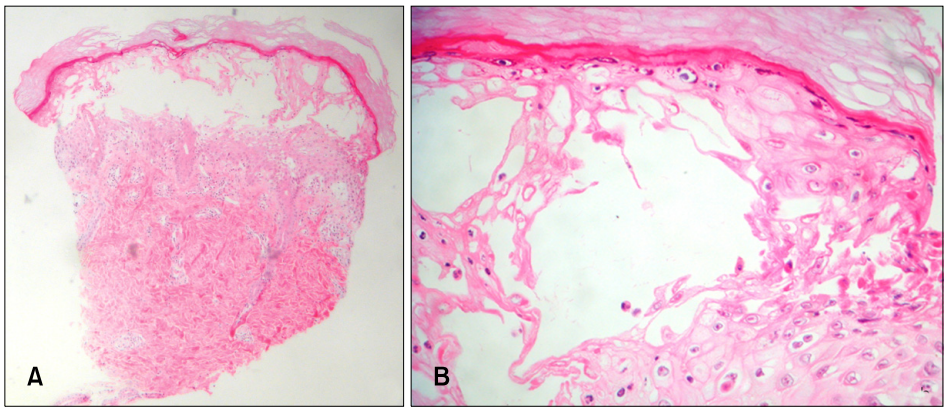


**Fig. 2.** (A) Multiple intraepidermal vesiculation and perivascular infiltration with predominant lymphocytes and few neutrophils within the dermis (H&E, ×40), (B) necrotic keratinocytes and infiltration within the vesicles consisting of lymphocytes and neutrophils (H&E, ×400).

seizure secondary to chemotherapy initiated one month previous for acute lymphocytic leukemia. The chemotherapy regimen consisted of prednisone, vincristine, daunorubicin, L-asparaginase, and methotrexate. Abdominal computed tomography performed prior to transfer to our facility showed diffuse edematous swelling of the pancreas and extensive peripancreatic fluid collection (Fig. 1A). Brain magnetic resonance imaging revealed bilateral asymmetric high-signal intensity in both temporo-occipital and parieto-occipital lobes with some cytotoxic edema in the right occipital lobe. Laboratory investigations revealed a white blood cell count of 1,520/mm$^3$, total bilirubin of 3.1 mg/dl (normal range, 0.2～1.0 mg/dl), direct bilirubin of 0.8 mg/dl (normal range, 0～0.5 mg/dl), amylase of 919 IU/L (normal range, 37～150 IU/L) and lipase of 2,559 U/L (normal range, 114～286 U/L). Acute pancreatitis had developed as the result of L-asparaginase complication and posterior reversible encephalopathy syndrome due to acute hypertensive encephalopathy or chemotherapeutic agents. Amlodipine was prescribed to control the hypertension. Chemotherapy was stopped and TPN was started to treat the acute pancreatitis. After one month, the patient was referred to the dermatology department for consultation regarding periorificial, reddish, eroded bullae with multiple vesicles and blisters on his fingers, toes, and buttock that had developed five days previously (Fig. 1B～D). Bullous disorders such as chronic bullous disease of childhood, herpetic whitlow, and hand-foot-mouth disease were suspected. A Tzanck test of the bullae was negative. A biopsy was subsequently performed of the bulla on the right second finger. Histopathology revealed necrotic keratinocytes with multiple intraepidermal vesicles and perivascular infiltration with predominant lymphocytes and few neutrophils within the dermis (Fig. 2). Based on the histopathological findings, bullous AE was suspected. The diagnosis was confirmed by chemistry results showing reduced serum zinc of 16.5 μg/dl (normal range, 66～110 μg/dl) and alkaline phosphatase (ALP) of 35 IU/L (normal range, 80～220 IU/L). Skin lesions improved rapidly within a few days of starting intravenous zinc sulfate supplementation.

## DISCUSSION

AE cases secondary to TPN have been reported previously[4,5]. TPN solutions contain glucose, amino acids, and principal electrolytes including Na, K, Cl, Ca, and Mg without vitamins and trace elements[4]. Therefore, in about two weeks, zinc levels decrease below the normal range and symptoms develop[6]. Zinc functions in the formation and maintenance of all tissues[7]. The skin includes approximately 6% of total body zinc[8]. In addition, zinc is an essential component of various metalloenzymes such as ALP, carbonic anhydrase, and RNA polymerase[7]. Of those elements, ALP is a readily available test that it worthwhile to perform[7]. In this case the decrease in ALP was indicative of its diagnostic value.

Keratinosomes are enriched in metalloenzymes and they control keratinization[9]. Therefore, zinc deficiency affects normal keratinization and gives rise to keratinocyte degeneration[10]. Histopathologically, bullous AE is accompanied by highly eosinophilic, necrotic keratinocytes, and intracellular edema bringing about intraepidermal vesiculation[3,11]. These histopathologic features of bullous AE distinguish it from spongiotic dermatitis. Cases of bullous AE show prominent vesiculation in the midst of absent to scant spongiosis, adjacent eosinophilic to necrotic keratinocytes, and primarily lymphoneutrophilic infiltration[3]. Histopathological findings in our case were consistent with bullous AE.

Recently, atypical histopathologic findings in a patient with Crohn's disease who presented with bullous AE were reported[12]. Skin biopsies revealed intraepidermal vesiculation with eosinophilic necrotic keratinocytes, marked vacuolar degeneration of basal keratinocytes, and lichenoid interface dermatitis. As a result, the authors initially considered lichenoid drug eruption with bullae formation; but the worsening skin lesions upon TPN shifted suspicion to zinc deficiency. Therefore the authors suggested that clinical suspicion of AE is more important than histopathologic findings in diagnosing AE.

Treatment for AE entails 3 mg/kg/day of elemental zinc supplement. Once replacement therapy is initiated, clinical manifestations improve within days to weeks[7]. In our case, there were multifactorial issues related to zinc deficiency including inadequate intake of zinc related to TPN, malabsorption caused by acute pancreatitis and methotrexate[13], and increased metabolism due to leukemia.

In conclusion, when using TPN, special attention should be paid to prevent zinc deficiency. Owing to the rarity of the disease, if clinicians do not initially suspect the bullous form of AE, diagnosis and treatment will be delayed; therefore, clinicians must consider bullous AE when they encounter bullous dermatosis. Skin biopsy is an essential component of the workup necessary to diagnose bullous AE.

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