Coma Blisters: A Case Report and Review of the Literature

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ABSTRACT:

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Coma blister is an uncommon cutaneous manifestation classically described following conditions causing impaired consciousness, most frequently associated with drugs like overdoses of central nervous system depressants. However, they have also been described in association with other non-drug related cases of impaired consciousness and even in the setting of non-comatose conditions. They clinically present as tense blisters or bullae, occasionally resembling erosions and violaceous plaques, few in number over normal or edematous skin. They can occur on both dependent and non-dependent areas of the trunk and extremities. Coma blisters typically appear within 24 hours after the onset of unconsciousness and resolves spontaneously within 10-14 days. The exact pathophysiology behind coma blisters remains controversial as it cannot be fully explained by pressure effects nor by toxic effects of any specific medication and no relation to any underlying infection or autoimmune condition have been found so far. The hallmark and the most frequent histopathological feature of the lesion consists of necrosis of the eccrine gland. There is

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no specific treatment available for coma blisters. We herein present a 49- year-old Thai male who developed bullae on his extremity after prolonged impairment of consciousness without any predisposing associated substance that could cause the bullae. We also reviewed the literature on coma blisters in adult as well as in pediatric patients in terms of clinical characteristics and histopathological findings.

Key words: Coma, blisters, histopathology

Introduction

Coma blister is an infrequent cutaneous manifestation traditionally related to barbiturate intoxication[1]. However, it can also be seen in the setting of unconsciousness due to other etiologies or even in non-comatose patients. The actual etiologies and pathogenesis are still unclear, but no association with underlying infections or autoimmune conditions have been elucidated so far[2-3]. Eccrine sweat gland necrosis is the hallmark of histopathological feature in coma blisters[4-5]. We present a 49- year-old Thai male who developed bullae on his extremity after prolonged impairment of consciousness without any predisposing associated substance that could cause the blisters.

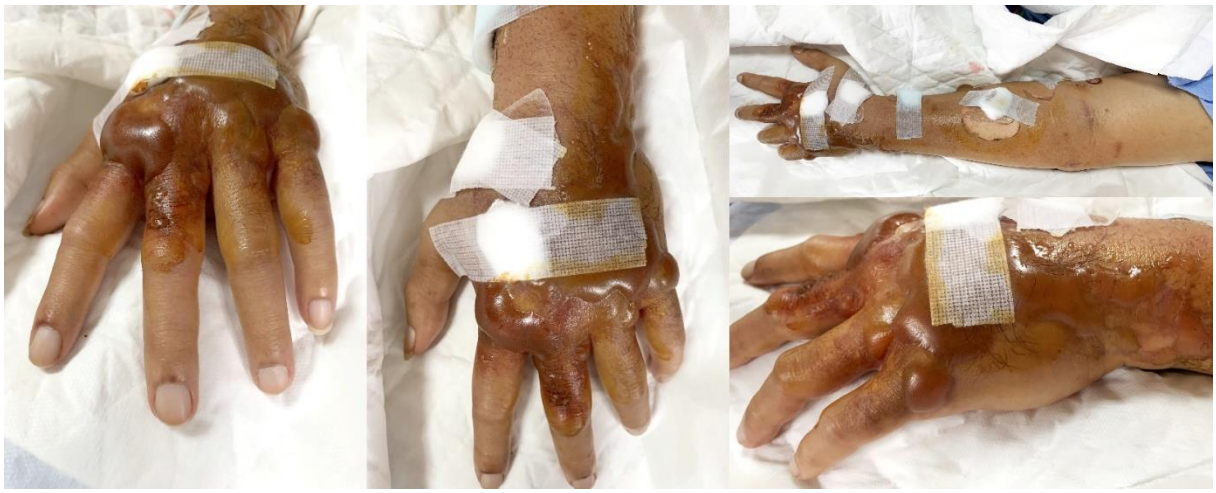

Figure 1 Extensor aspect of the left forearm and left dorsal hand showing multiple tense bullae and few erosions on normal-appearing skin.

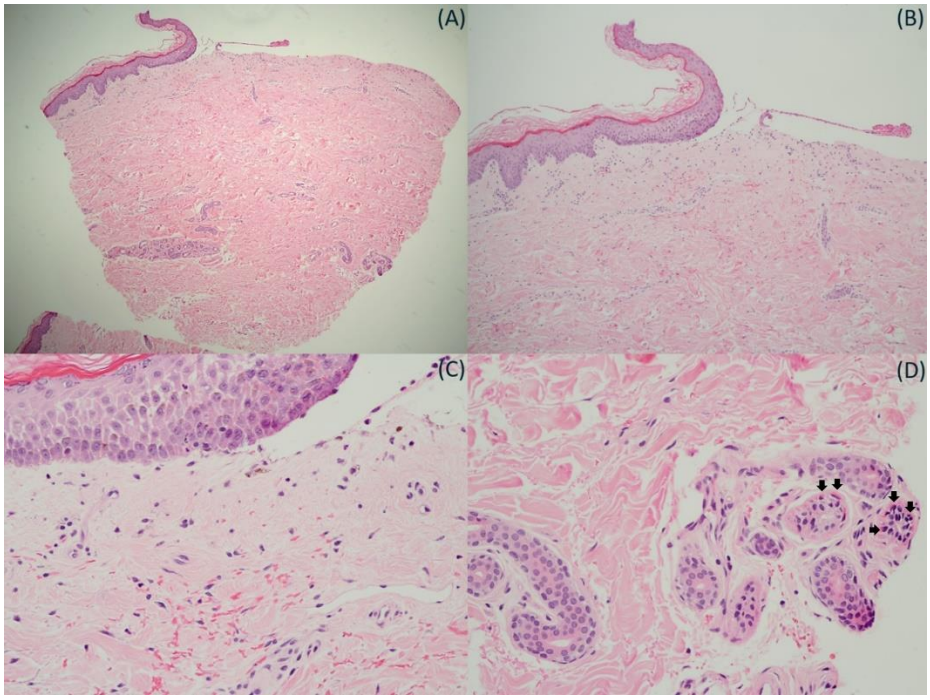

Figure 2 Histological findings **A** Subepidermal blistering. HE. X40. **B** Sparse superficial perivascular and interstitial inflammatory cells infiltration. HE. X100. **C** Inflammatory cells mainly compose of lymphocyte with some red blood cell extravasation. HE. X400. **D** Eosinophilic necrosis of the sweat gland. (black arrows) HE. X400.

Case report

A 49-year-old Thai male with underlying type 2 diabetes mellitus, hypertension, dyslipidemia, ischemic heart disease and post-cardiac arrest who underwent single-chamber implantable cardioverter-defibrillator implantation presented to the emergency department with dyspnea and syncope with the spontaneous recovery of consciousness. At the emergency room, physical examination revealed fine bilateral crackles on lung auscultation and marked pitting edema of both the legs. Other physical examinations were unremarkable. The diagnosis of congestive heart failure precipitating cardiac syncope was made. During hospitalization, there was a prolonged episode of ventricular tachycardia with intractable cardiac arrest lasting approximately 60 minutes in duration. The patient was defibrillated for multiple sessions, given various doses of epinephrine, 2% lidocaine HCl, and amiodarone for resuscitation and anti-arrhythmia. He was placed on extracorporeal membrane oxygenation

and intra-aortic balloon pump via his left and right femoral vessels, respectively. He developed pallor of the legs along with diminished pulse on the left side. Acute limb ischemia was diagnosed, and embolectomy was done on the same day. Following that, postoperative compartment syndrome was noted on his left leg, so fasciotomy operation was performed. The patient remained intubated due to prolonged coma. Furthermore, he subsequently developed seizure but cranial magnetic resonance imaging displayed no abnormalities. The lidocaine induced seizure was controlled with intravenous levetiracetam. Five days after coma, multiple tense bullae appeared on the patient's extremity. Dermatological examination revealed numerous tense bullae and few erosions on normal-appearing skin on the left forearm and left dorsal hand. (Figure 1) Nikolsky's sign was negative. Gram stain from the bullous fluid and Tzanck smear from the base of bullae were negative. Histopathological examination demonstrated subepidermal blister with superficial perivascular and interstitial lymphocyte infiltration with some red blood cell extravasation. (Figure 2) Besides that, sweat gland necrosis was noted on higher magnification power. The skin lesions were treated with appropriate wound care and topical sodium fusidate ointment. After 1 week, the bullae improved, and no new skin lesions developed. Unfortunately, on day 17 of the admission, the patient passed away from persistent arrhythmia.

Discussion

In 1812, coma blisters were initially described among soldiers of the French Revolution who developed carbon monoxide induced coma. Coma bullae have subsequently been associated with drug-induced coma over the years. The common drug-associated being barbiturate and benzodiazepine. Infrequent association with other substances such as tricyclic antidepressants, opioids, phenothiazines, methadone, antipsychotics, heroin, and alcohol have been implicated as well[2]. Nevertheless, this condition can occur in non-drug related causes of prolonged impairment of consciousness, central nervous system diseases (such as meningitis, tumor, stroke) and metabolic disorders (such as diabetic ketoacidosis). Although, mostly associated with comatose state, they can also be seen in the setting of non-comatose conditions with other etiologies such as immobilization, secondary to trauma[2-7]. (Table 1)

Its exact pathophysiology is still not well established, nonetheless, it is hypothesized to be multifactorial in origin. Pressure and tissue ischemia were described as the pivotal cause for this phenomenon since the blisters often localized at pressure sites[8]. Even so, this would not explain the distribution of bullae on non-

pressure related areas in many other cases. Thus, other possible explanations of the blister are the role of autonomic instability in comatose state, the severe toxic effect of some medications, changes in vasomotor control and immune-mediated mechanisms even in the state of immobility[3]. Prolonged immobility may lead to pressure-induced anoxia and injury of skin[1,4,9-10]. Similarly, our patient had evidence of prolonged immobility in setting of unconsciousness with no obvious evidence of predisposing coma blister associated substance.

Table 1 Summary of case reports of coma blisters in adults

Author/ year	Age/ Sex	Consciousness level	Systemic disease	Drug-relation	Onset after cause	Blister site	Pressure site	Histopathology
Holden[8]/ 1977	37/ F	Coma	-	Barbiturate	4 days	Forearm Trunk	N/A	Striated muscle necrosis
	46/ M	Coma	-	Barbiturate Diazepam Alcohol	N/A	Hands Trunk	N/A	Muscle necrosis
Herschthal[14]/ 1979	23/ F	Coma	-	Amitriptyline Clorazepate	N/A	Knee Foot	N/A	Intraepidermal vesicle Sweat gland necrosis
Brendan[15]/ 1999	37/ M	Confusion	-	Amitriptyline	2 days	Arm Trunk	N/A	Subepidermal splitting
Maguiness[16]/2002	26/ F	Coma	-	Amitriptyline	N/A	Hand Face Shoulder	N/A	Epidermal necrosis Follicular necrosis Vasculitis
You[17]/ 2002	37/ M	N/A	-	Alcohol	N/A	Face Trunk Extremities	Yes	Intraepidermal blister Sweat gland necrosis
Tsokos[18]/ 2002	44/ F	Death	-	Theophylline	N/A	Forearm	Yes	Subepidermal blister Sweat gland necrosis
Kim[19]/ 2002	53/ M	Semi coma	-	Alcohol	3 days	Back Buttocks Extremities	Yes	Subepidermal blister Sweat gland necrosis Thrombosis of vessel
Ferreli[20]/ 2003	41/ F	Normal	-	N/A	N/A	AbdomenThigh	N/A	Epidermal necrosis Sweat and sebaceous gland necrosis
Keng[21]/ 2006	29/ F	Lethargy	-	Phenobarbital	1 day	Hands	N/A	Nonspecific findings
Waring[13]/ 2007	53/ F	Coma	-	Acetaminophen Codeine	1 day	Forearm	N/A	N/A
Rocha[22]/ 2009	29/ M	Coma	Infectious meningoencephalitis	-	2 days	Hands	N/A	Intraepidermal vesicle Thrombosis of vessel

Table 1 Summary of case reports of coma blisters in adults (continue)

Piede[3]/ 2011	**49/ M**	**Normal**	**Wegener granulomatosis**	**-**	**N/A**	**Lower extremities**	**N/A**	**Vascular thrombi Sweat gland necrosis**
Muirhead[23]/2011	54/ F	Coma	Rhabdomyolysis	Opiates TCA benzodiazepines	N/A	Abdomen	No	Epidermal necrosis
Kim[11]/ 2011	46/ M	Coma	-	Alcohol	12 hours	Arm	N/A	Epidermal necrosis Sweat gland necrosis
Branco[24]/2011	45/ F	Coma	Rhabdomyolysis	Phenobarbital	N/A	Knee Hand Shoulder Arm, foot	N/A	Epidermal necrosis Intraepidermal vesicle Sweat gland necrosis
Agarwal[25]/ 2012	24/ F	Abnormal	Respiratory failure	-	2 days	Hand Arm	N/A	Subepidermal blister Sweat gland necrosis
Chacon[12]/ 2013	18/ M	Under general anesthesia	Postoperative	Sedative medications	2 days	Arm	N/A	Subepidermal blister Sweat gland necrosis
Wiegand[26]/ 2013	27/ M	Coma	Rhabdomyolysis	Quetiapine	N/A	Ankle Thigh	Yes	N/A
Asokan[27]/2014	42/ M	Coma	Rhabdomyolysis	Alcohol	N/A	Trunk Forearms Legs Face	Yes	Intraepidermal vesicle Sweat gland necrosis
Chang[28]/ 2016	40/ M	Coma	Rhabdomyolysis	-	1 day	Forearm Hand	N/A	N/A
Ruiz-Rivero[29]/ 2017	49/ M	Coma	-	TCA Opiates Benzodiazepine	2 days	Legs Feet Hand	N/A	Sweat gland necrosis
Present study	49/ M	Coma	-	-	5 days	Upper extremity	No	Subepidermal blister Sweat gland necrosis

Coma blisters in adult patients are relatively well known. On the other hand, it has rarely been reported in pediatrics. (Table 2) Characteristically, the cutaneous lesions, manifest as tense bullae adjacent to normal-appearing skin, occurring in both pressure and non-pressure areas mainly over the extremities and trunk. Other skin lesions described were erythematous macules and plaques, often preceding the onset of bullae. Cutaneous lesions typically present within 12-96 hours after loss of consciousness[8,11]. The distribution of bullae in our patient was also comparable to previous studies of coma blisters[7,9,23]. Whereas, the time of onset of the lesions in present studies was quite longer than most of prior data[11,13,15]. The review of literatures found the various of cause-association, duration of onset, distributions of lesions as well. (Table 1) Differential diagnosis may include infectious process and other inflammatory etiologies (e.g., edema blister, bullous diabeticorum, friction and postburn blister, and bullous drug eruptions). A clinical diagnosis can often be made, but correlation with histopathology is recommended.

The histological evaluation demonstrates the pathognomonic feature of eccrine necrosis in coma bullae. (Table 1) Correspondingly, our patient's hematoxylin and eosin staining also demonstrated sweat gland necrosis[4-5]. Based on the previous histopathological study, the inner cell layer of the eccrine ducts are affected the earliest[11]. However, absence of eccrine necrosis does not exclude the diagnosis since there were other patterns including subepidermal bullae and focal necrosis in the epithelium of pilosebaceous follicles as well. The degree of inflammation could be minimal to moderate or even absent. Dermal eosinophil infiltration was reported as one of the clues pointing towards a drug-related etiology. Vascular thrombi in the dermis were also occasionally described as another significant histological evidence of drug association[4-6,12]. Direct immunofluorescence staining was not carried out in this study. While, most direct immunofluorescence studies revealed nonspecific patterns, thus pointing away from an immune mediated pathogenesis[10]. Coma blister is considered a benign condition due to its self-limiting course. It usually heals within 1-4 weeks with an intact healthy skin. Therefore, the management should not only be improvement of a patient's underlying condition but also appropriate wound care with topical antibiotics to prevent secondary infections without the need of any specific treatment[12-13].

Table 2 Summary of case reports of coma blisters in pediatrics

Author/ year	Age/ Sex	Consciousness level	Systemic disease	Drug-relation	Onset after cause	Blister site	Pressure site	Histopathology
Mehregan[2]/ 1992	12/ F	Coma	Diabetic ketoacidosis	No	1 day	Buttocks Face Hand	Both	Epidermal necrosis Sweat gland necrosis
Setterfield[30]/ 2000	4/ F	Coma	Epilepsy	Clobazam	N/A	Elbow	Yes	Sweat gland necrosis
Kim[19]/ 2002	4/ M	Coma	-	No	2 days	Back Buttocks Extremities	Yes	Subepidermal blister Sweat gland necrosis Thrombosis of vessel
Basu[9]/ 2009	9/ M	Drowsiness	-	Valproate	N/A	Thigh Trunk Ear	No	Subepidermal blister Sweat gland necrosis
	16 mo/ F	Drowsiness	-	Clonazepam	N/A	Ear	No	N/A
Bosco[7]/ 2012	11/ M	Coma	Infectious meningoencephalitis	No	N/A	Legs Trunk	No	Subepidermal blister Sweat gland necrosis Thrombosis of vessel
Chacon[12]/ 2013	5 mo/ M	Under general anesthesia	Postoperative	N/A	2 days	Extremities Arm	N/A	Subepidermal blister Sweat gland necrosis

In conclusion, coma blisters should always be considered in unconscious patients presenting with bullae. A high level of recognition is needed since this disease responds well with the improvement of the consciousness and underlying condition.

References

1. Beveridge GW, Lawson AAH. Occurrence of bullous lesions in acute barbiturate intoxication. Br Med J 1965;1:835-7.
2. Mehregan DR, Daoud M, Rogers R. Coma blisters in a patient with diabetic ketoacidosis. J Am Acad Dermatol 1992;27:269-70.
3. Piede J, Wallace E. Coma Bullae: Associations Beyond Medications. Mayo Clin Proc 2011;86:e5.
4. Sánchez Yus E, Requena L, Simón P. Histopathology of cutaneous changes in drug-induced coma. Am J Dermatopathol 1993;15:208-16.
5. Kato N, Ueno H, Mimura M. Histopathology of cutaneous changes in non-drug-induced coma. Am J Dermatopathol 1996;18:344-50.
6. Arndt KA, Mihm MC, Parrish JA. Bullae: a cutaneous sign of a variety of neurologic diseases. Invest Dermatol 1973;60:312-20.
7. Bosco L, Schena D, Colato C, Biban P, Girolomoni G. Coma blisters in children: case report and review of the literature. J Child Neurol 2012;28:1677-80.
8. Holden CA. Cutaneous bullae in coma due to poisoning: an association with deep seated ischaemic lesions of muscle. Anaesthesia 1977;32:554-5.
9. Basu A, Brown S, Kirkham N, Ramesh V, Leech S, Devlin A. Coma blisters in 2 children on anticonvulsant medication. J Child Neurol 2009;24:1021-5.
10. Reiley GD, Harrington CI. Positive immunofluorescence in bullous lesions in drug-induced coma. Br J Dermatol 1983;109:720–4.
11. Kim GW, Park HJ, Kim HS, et al. Bullae and sweat gland necrosis in the differential diagnosis for Vibrio vulnificus infection in an alcoholic patient. J Korean Med Sci 2011;26:450-3.
12. Chacon AH, Farooq U, Choudhary S, et al. Coma Blisters in Two Postoperative Patients. Am J Dermatopathol 2013;35:381-4.
13. Waring WS, Sandilands EA. Coma blisters. Clin Toxicol 2007;45:808-9.
14. Herschthal D, Robinson MJ. Blisters of the Skin in Coma Induced by Amitriptyline and Clorazepate Dipotassium. Arch Dermatol 1979;115:499.
15. Fogarty BJ, Khan K. Drug induced blistering and the plastic surgeon: a case of amitriptyline induced skin necrosis. Burns 1999;25:768-70.
16. Maguiness S, Guenther L, Shum D. Coma blisters, peripheral neuropathy, and amitriptyline overdose: A brief report. J Cutan Med Surg 2002;6:438-41.
17. You MY, Yun SK, Ihm W. Bullae and Sweat Gland Necrosis After an Alcoholic Deep Slumber. Cutis 2002;69:265-8.
18. Tsokos M, Sperhake JP. Coma Blisters in a Case of Fatal Theophylline Intoxication. Am J Forensic Med Pathol 2002;23:292-4.

19. Kim KJ, Suh HS, Choi JH, Sung KJ, Moon KC, Koh JK. Two cases of coma-associated bullae with eccrine gland necrosis in patients without drug intoxication Acta Derm Venereol 2002;82:378–80.
20. Ferreli C, Sulica VI, Aste N, et al. Drug-induced sweat gland necrosis in a non-comatose patient: a case presentation. J Eur Acad Dermatol Venereol 2003;17:443–5.
21. Keng M, Lagos M, Liepman MR, Trever K. Phenobarbital-Induced Bullous Lesions in a Non-Comatose Patient. Psychiatry 2006;3:65-9.
22. Rocha J, Pereira T, Ventura F, Pardal F, Brito C. Coma Blisters. Case Rep Dermatol 2009;1:66–70.
23. Muirhead T, Rudner E, Lim HW. A case of coma blisters in a non-pressure dependent distribution. J Am Acad Dermatol 2011;64 Suppl 1:AB95.
24. Branco MM, Capitani EM, Cintra ML, Hyslop S, Carvalho AC, Bucaretchi F. Coma blisters after poisoning caused by central nervous system depressants: Case report including histopathological findings. An Bras Dermatol 2012;87:615-7.
25. Agarwal A, Bansal M, Conner K. Coma blisters with hypoxemic respiratory failure. Dermatol Online J 2012;18:10.
26. Wiegand TJ, Gorodetsky RM, Peredy TR. Coma Blisters in the Setting of Quetiapine Overdose: Case Report and Review of Literature. Asia Pac J Med Toxicol 2013;2:153-6.
27. Asokan N, Binesh VG, Andrews AM, Jayalakshmi PS. Bullous Lesions, Sweat Gland Necrosis and Rhabdomyolysis in Alcoholic Coma. Indian J Dermatol 2014;59:632.
28. Chang KS, Su YJ. Coma blister in nontraumatic rhabdomyolysis. Am J Emerg Med 2016;34:1324.e1-2.
29. Ruiz-Rivero J, Pulido-Perez A, Suarez-Fernandez RM. Coma blisters with deep soft tissue involvement after drug overdose. Int J Dermatol 2017;56:881-3.
30. Setterfield JF, Robinson R, MacDonald D, Calonje E. Coma-induced bullae and sweat gland necrosis following clobazam. Clin Exp Dermatol 2000;25:215-8.