Case Report

Necrotizing Skin and Soft-Tissue Infections Associated with Septicemia: 7 Cases Report and Review

Sunisa Thaichinda MD*,
Narongdet Kositpantawong MD**

** Division of Dermatology, Department of Medicine, Hat Yai Hospital, Songkhla*
*** Department of Medicine, Hat Yai Hospital, Songkhla*

The authors report seven cases of necrotizing skin and soft- tissue infections, with clinical presenting as hemorrhagic bullae, gangrenous cellulitis or necrotizing fasciitis, in association with septicemia, between January 2003 and January 2007 in Hat Yai Hospital. Six were male and the majority of the lesions, six cases, occurred in the lower extremities. The average age of the patients was 50.0 ± 11.019 years old. All patients presented with watery diarrhea, severe abdominal pain, high fever and sepsis. The skin lesions were begun with erythema, tender, and swelling with formation of hemorrhagic bullae, gangrene and necrosis within 24-48 hours. Three of them were caused by Streptococcus spp., another three by Halophilic Vibrios, and only one by Aeromonas hydrophila. Furthermore, the literatures related with clinical manifestations of necrotizing skin and soft-tissue infections, etiologic pathogens, histological finding, management in setting of sepsis, co-morbid conditions, complications and patients' outcome were reviewed.

Keywords: *Necrotizing skin and soft-tissue infections, Hemorrhagic bullae, Gangrenous cellulitis, Necrotizing fasciitis, Septicemia*

J Med Assoc Thai 2008; 91 (1): 117-23
Full text. e-Journal: *http://www.medassocthai.org/journal*

Necrotizing skin and soft-tissue infections have been recognized and reported for centuries, characterized by localized painful erythema and edema, rapidly progressing to cyanosis, blistering and necrosis with deep gangrene and sloughing of tissue. It is accompanied with significant systemic toxicity and high mortality[1-16]. They are varying in anatomical location, tissue level of involvement, offending organisms, together with factors of the host result in a variety of presentations, clinical course and prognosis. This confusion is related to the naming of necrotizing infections based upon clinical features such as hemorrhagic bullae, gangrenous cellulitis or necrotizing fasciitis instead of surgical or pathological diagnosis.

The relatively uncommon local necrotizing infections that involve skin and soft tissues in conditions of sepsis or septicemia, with various risk factors, will be performed.

Correspondence to : Thaichinda S, Division of Dermatology, Department of Medicine,Hat Yai Hospital, Songkhla 90110, Thailand. Phone: 074-273-100, Fax: 074-273-218, 074-273-252. E-mail: bombergirl_16@hotmail.com

Material and Method

Between January 2003 and January 2007 in Department of Medicine, Hat Yai Hospital in Southern Thailand, seven patients with skin and soft-tissue infections with septicemia were diagnosed. Septicemia is defined as the abrupt onset of symptoms and signs of systemic inflammatory response syndrome and presence of viable bacteria or their toxins in the blood.

The authors collected all data from the medical records including age, sex, site of origin of infection, present illness, pre-existing condition, complication, medical add on surgical management, offending organisms, length of stay and patients' outcome. Histopathological study was performed in four patients.

Results

There were six males and one female, the mean age was 50.0 ± 11.019 years, range from 38 to 66 years. Common organ involved by these necrotizing skin and soft- tissue infections were lower extremities as demonstrated in Fig. 1 to 6, except one which was seen in the oral cavity (Fig. 7). All patients presented

Fig. 1 Case No. 1: Streptococcal gangrene: skin necrosis and eschar precede sloughing of tissues

Fig.4 Case No. 4: Vibrio vulnificus cellulitis and hemorrhagic plaques and bullae on left ankle and leg

Fig. 2 Case No. 2: Severe pain,erythema and edema with formation of bullae in Streptococcus pneumoniae septicemia

Fig. 5 Case No. 5: Right leg with hemorrhagic bullae Cultures of bullae were positive for Streptococus pneumoniae

Fig. 3 Case No. 3: Purpura and hemorrhagic vesiculobullous eruption involving several area of her thighs and legs in patient with Aeromonas hydrophila septicemia

Fig. 6 Case No. 6: Large serosanguineous bullae at the calf of right leg before fasciotomy in Vibrio parahemolyticus septicemia

Fig. 7 Case No. 7: Purpuric patches and hemorrhagic bullae at oral cavity and tongue in the patient with Vibrio parahemolyticus septicemia
He died within 36 hrs after ingestion of raw seafood

with watery diarrhea, severe abdominal pain, high fever, tenderness at the site of skin lesions and sepsis. The skin lesions were begun with severe pain and rapidly progressive erythema and swollen with formation of hemorrhagic bullae and gangrenous cellulitis within 24-48 hours. Incisional skin biopsies and culture were performed in four patients.

The histopathology of the specimens revealed necrosis of the epidermis and sub-epidermal bulla formation (Fig. 8) with extravagated of red blood cells and massive infiltration of neutrophils in the dermis and subcutis (Fig. 9). Thrombosis and suppuration of blood vessel were noted. Common pre-existing medical condition in these patients was alcoholic cirrhosis, in four cases; the others were hepatic cirrhosis, hypersplenism, and Cushing syndrome. Three of them were caused by *Streptococcus* spp., another three by *Halophilic Vibrios,* and only one by *Aeromonas hydrophila*. In spite of aggressive management, three patients developed multisystem organ failure leading to death.

Discussions

The diagnosis of necrotizing skin and soft-tissue infections were first made by clinical findings as: *hemorrhagic bullae*, *gangrenous cellulitis*, or *necrotizing fasciitis*. The affected area develops erythematous tender, warm, swollen, subsequently

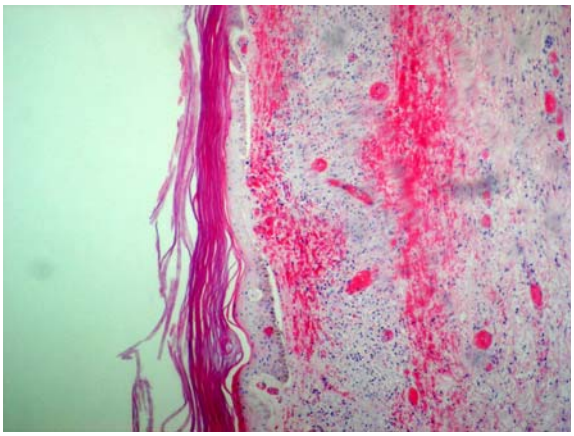

Fig. 8 Subepidermal bullae and dermal infiltration composed of predominant neutrophils (hematoxylin-eosin, x40)

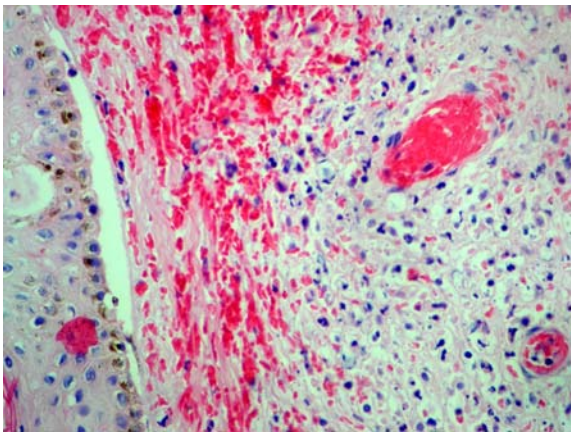

Fig. 9 Bullous formation with extravasation of red blood cell and massive infiltration of neutrophils in the dermis and subcutis (hematoxylin-eosin, x100)

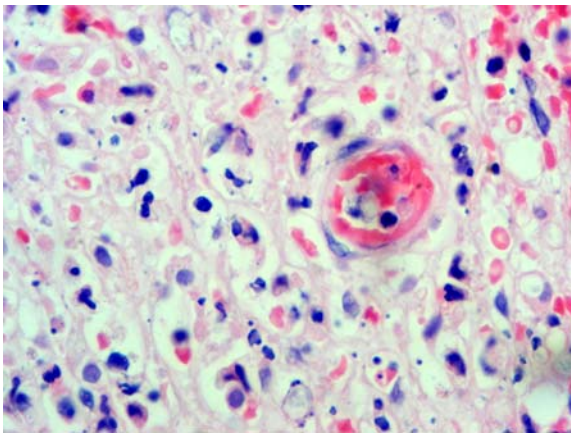

Fig. 10 Thrombosis of blood vessels (hematoxylin-eosin x400)

Table 1. Clinical summaries of 7 patients with necrotizing skin and soft-tissue infection and septicemia

Pt. No.	Patient Age/Sex	Site of skin lesions	Occu-pation	Present illness fever with	Pre-existing conditions	compli-cations	Aspirate bleb (1) gram stain, or (2) C/S	Skin biopsy C/S	Blood C/S	Medication	Surgery	Length of stay	Outcome
1	38/M	Both legs both arms	Worker	Watery diarrhea	Alcoholic cirrhosis	DIC	(1) Gram +ve cocci, in chain	beta-Streptococcus group A	beta-Streptococcus group A	PGS/ Cefotaxime iv	Dressing debridement	21 days	Complete recovery
2	48/M	Both feet	Worker	Watery diarrhea	Alcoholic cirrhosis	DIC ARF	(2) Strep. pneumoniae	Strep. pneumoniae	Strep. pneumoniae	Cefeprime iv	Dressing debridement	15 days	Complete recovery
3	64/F	Both legs	House wife	Watery diarrhea	Cirrhosis and hypersplenism	DIC ARF	(1) Gram neg bacilli (2) Aeromonas hidrophila	Not done	Aeromonas hidrophila	Amoxicillin-Clavulanic acid/ Ciprofloxacin iv	Not done	1 day	Death
4	41/M	Left ankle Left leg	Merchant	Watery diarrhea	Hepatitis B related cirrhosis	DIC ARF Encep	(1) Gram stain not found (2) Vibrio vulnificus	Not done	Vibrio vulnificus	Cetriaxone/ Ciprofloxacin iv FFP	Several dressing	12 days	Death
5	38/M	Both legs	Merchant	Watery diarrhea/ Neck swelling	DM alcoholic cirrhosis	DIC ARF GIB ARDS	(1) gram +ve cocci, single, pair, chain	beta-Streptococcus group A	beta-Streptococcus group A	Amoxicillin-Clavulanic acid iv/ CPR/ Clindamycin iv	Several dressing	9 days	Death
6	55/M	Rt. leg	Gardener	Diarrhea severe abd. pain	Psoriasis/ Cushing syndrome	-	(2) Vibri parahaemolyticus (leg & rectal)	Vibrio parahaemolyticus	Vibrio parahaemolyticus	Cetriaxone iv then Imipenem iv	Median fasciotomy	9 days	Complete recovery
7	66/M	Oral/ Tongue	Gardener	Watery diarrhea	Alcoholic cirrhosis	DIC ARF	(2) Vibrio parahaemolyticus	Not done	Vibrio parahaemolyticus	Imipenem iv/ CPR	Not done	4 hours	Death

Serum sample were collected at day 1 and skin culture and biopsy were performed on day 2 or 4

DIC = disseminated intravascular coagulation, ARF = acute renal failure, ARDS = adult respiratory distress syndrome, Encep = encephalitis, GIB = gastro-intestinal bleeding, C/S = culture, FFP = fresh frozen plasma, CPR = cardio-pulmonary resuscitation, iv = intravenous route, PGS = penicillin G sodium

bullae appear, initially filled with clear fluid, but rapidly becoming hemorrhagic or violaceous, signifying dermal necrosis[13,21]. The infections are often associated with severe systemic toxic reactions, and rapidly fatal. Hemorrhagic bullae occur secondary to involvement of small vessels supplying the skin or results from infection with gas –forming strain of bacteria - eg. Escherichia coli, Klebsiella spp, Aeromonas hydrophila, or Bacteroides species, or aerobic and anaerobic streptococci[18,19], and Halophilic Vibrios bacteria[11,12]. Gangrenous cellulitis is a localized bacterial infection commonly involving the dermis and subcutaneous layers, most likely resulting from a disturbance in the skin surface. Necrotizing fasciitis is a soft tissue infection caused by toxin producing virulent bacteria, which is characterized by widespread fascial necrosis with relative sparing of the skin and underlying muscle[13]. The most common invading bacteria is group A Streptococcus which has been classified as necrotizing fasciitis type II, whereas the other polymicrobial pathogens as necrotizing fasciitis type I[15,16,22].

The common portal of entry of organisms in the present was minor skin and soft-tissue trauma[18,19,21,22]. Aeromonas hydrophila septicemia may follow penetrating trauma in fresh or brackish-water environment. The Vibrio septicemia seemingly developed the diseases via abrasion or open skin lesions exposed to sea water or shellfish. Case number 7 with very poor oral hygiene had a recent history of ingesting raw seafood.

Skin biopsy for pathological examination and culture is an alternative method of obtaining diagnosis but is only 20% useful in selected cases[5,22]. The histological finding of the skin lesions in the *initial stage of erythema* and localized swelling revealed edema, massive infiltration of neutrophils and extravasation of red blood cells. The *bullous lesions* showed subepidermal bullae and vasculitis. The *gangrenous lesions* showed necrosis of the skin surface and non-leukocytoclastic, transmural, necrotizing vasculitis with or without thrombosis in the subcutis. Bacteria may be present throughout the dermis, and within the bullous fluid or around the dermal vessels[5,9,11,20-23].

Accurate clinical diagnosis and aspiration of bleb, Gram stain and culture should be performed. The treatments must include early surgical intervention, systemic antibiotics and hemodynamic support. Repeated explorations and debridement are necessary to define the extent of disease and resect all necrotic tissues. Choice of antibiotics is based on identification and sensitivity of organism isolated[13,18]. Empiric antibiotics should cover aerobic and anaerobic organisms. Ampicillin-sulbactam plus clindamycin or metronidazole is a good first choice. For patients who have been hospitalized previously, gram-negative coverage should be improved by a third generation cephalosporin, carbapenem, fluoroquinolone, or an aminoglycoside[13,17-19,22]. If group A streptococcal infection is suspected, the combination of clindamycin, and penicillin were recommended. Intravenous immune globulin, high-dose (2 gm/kg), along with an antibiotic is a desirable therapeutic goal when hypotension is present. Antimicrobial agents against Halophilic Vibrios infections are tetracycline; fluoroquinolones (e.g. ciprofloxacin); third-generation cephalosporins (eg. ceftazicime); and aminoglycosides (e.g. gentamicin)[9,13].

Necrotizing skin and soft-tissue infections occur in patients with at least one of the following underlying diseases states: diabetes mellitus, cancer, malnutrition, liver diseases, chronic corticosteroid use, HIV infection, IV drug user and patients with peripheral vascular diseases[12] and vascular insufficiency[14,16]. These factors cause decreased immunologic defenses, allowing for more rapid spread of the infection or contribute to the setting of local tissue ischemia. Patients with cirrhosis also have portal hypertension, allowing bacteria to translocate from the gastrointestinal tract to bypass the phagocytic reticulo-endothelial system in the liver, and increased susceptibility to spontaneous bacteremia, with depressed level of serum complement and impaired iron metabolism[7,17,18,22].

There are many complications following these diseases such as acute renal failure, adult respiratory distress syndrome or other respiratory failure, delay in diagnosis, delay in first debridement, inadequate debridement, multiorgan system dysfunction, wound infection or other infections, and opportunistic fungal infestation[14,18]. Failure to control the infection at the time of the first operation will increase the mortality to 71%[13]. In the present study, the complications that lead to death were delayed and inadequate debridement and development of disseminated intravascular coagulation.

Conclusion

It is very important to make an early bedside diagnosis of all cutaneous manifestations of necrotizing skin and soft tissues infections in patients with systemic toxicity or florid sepsis, and several co-morbid condition such as liver cirrhosis, diabetes mellitus or other immune compromised conditions. Aggressive

resuscitation, adequate rapid debridement, obtaining material for appropriate cultures and systemic broad spectrum antibiotics must be given promptly, to reduce the associated morbidity and mortality of the disease, before life-threatening complications supervene.

Acknowledgment

The authors wish to thank Dr Sauvarat Auepemkiate MD, Department of Pathology, Faculty of Medicine, Prince of Songkhla University, for her kindness in performing the histological examination of skin biopsy specimen in this paper.

References

1. Wickboldt LG, Sanders CV. Vibrio vulnificus infection. Case report and update since 1970. J Am Acad Dermatol 1983; 9: 243-51.
2. Hurwitz RM, Leaming RD, Horine RK. Necrotic cellulitis. A localized form of septic vasculitis. Arch Dermatol 1984; 120: 87-92.
3. Leppard BJ, Seal DV, Colman G, Hallas G. The value of bacteriology and serology in the diagnosis of cellulitis and erysipelas. Br J Dermatol 1985; 112: 559-67.
4. Tyring SK, Lee PC. Hemorrhagic bullae associated with Vibrio vulnificus septicemia. Report of two cases. Arch Dermatol 1986; 122: 818-20.
5. Hook EW III, Hooton TM, Horton CA, Coyle MB, Ramsey PG, Turck M. Microbiologic evaluation of cutaneous cellulitis in adults. Arch Intern Med 1986; 146: 295-7.
6. Carlson KC, Mehlmauer M, Evans S, Chandrasoma P. Cryptococcal cellulitis in renal transplant recipients. J Am Acad Dermatol 1987; 17: 469-72.
7. Kielhofner MA, Brown B, Dall L. Influence of underlying disease process on the utility of cellulitis needle aspirates. Arch Intern Med 1988; 148: 2451-2.
8. Umbert IJ, Winkelmann RK, Oliver GF, Peters MS. Necrotizing fasciitis: a clinical, microbiologic, and histopathologic study of 14 patients. J Am Acad Dermatol 1989; 20: 774-81.
9. Bernard P, Bedane C, Mounier M, Denis F, Catanzano G, Bonnetblanc JM. Streptococcal cause of erysipelas and cellulitis in adults. A microbiologic study using a direct immunofluorescence technique. Arch Dermatol 1989; 125: 779-82.
10. Sachs MK. Cutaneous cellulitis. Arch Dermatol 1991; 127: 493-6.
11. Park SD, Shon HS, Joh NJ. Vibrio vulnificus septicemia in Korea: clinical and epidemiologic findings in seventy patients. J Am Acad Dermatol 1991; 24: 397-403.
12. Howard RJ, Bennett NT. Infections caused by halophilic marine Vibrio bacteria. Ann Surg 1993; 217: 525-30.
13. Sutherland ME, Meyer AA. Necrotizing soft-tissue infections. Surg Clin North Am 1994; 74: 591-607.
14. Hally RJ, Rubin RA, Fraimow HS, Hoffman-Terry ML. Fatal Vibrio parahemolyticus septicemia in a patient with cirrhosis. A case report and review of the literature. Dig Dis Sci 1995; 40: 1257-60.
15. McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA. Determinants of mortality for necrotizing soft-tissue infections. Ann Surg 1995; 221: 558-63.
16. Green RJ, Dafoe DC, Raffin TA. Necrotizing fasciitis. Chest 1996; 110: 219-29.
17. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg 1996; 224: 672-83.
18. Andreasen TJ, Green SD, Childers BJ. Massive infectious soft-tissue injury: diagnosis and management of necrotizing fasciitis and purpura fulminans. Plast Reconstr Surg 2001; 107: 1025-35.
19. Levine N. Kunkel M, Nguyen T Ackerman L. Emergency department dermatology. Curr Probl Dermatol 2002; 14: 183-220.
20. Dahl PR, Perniciaro C, Holmkvist KA, O'Connor MI, Gibson LE. Fulminant group A streptococcal necrotizing fasciitis: clinical and pathologic findings in 7 patients. J Am Acad Dermatol 2002; 47: 489-92.
21. Swartz MN, Weinberg AN. Bacterial diseases with cutaneous involvement. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz S, editors. Fitzpatrick's dermatology in general medicine. 6th ed. New York: McGraw-Hill; 2003: 1843-911.
22. Vinh DC, Embil JM. Rapidly progressive soft tissue infections. Lancet Infect Dis 2005; 5: 501-13.
23. Lucas S. Bacterial diseases. In: Elder DE, Elenitsas R, Johnson BL, Murphy GF, editors. Lever's histopathology of the skin. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2005: 551-60.

การติดเชื้อรุนแรงจนเกิดการอักเสบเน่าตายของผิวหนังและเนื้อเยื่ออ่อนร่วมกับ ภาวะเลือดเป็นพิษ เหตุติดเชื้อ: รายงานผู้ป่วย 7 ราย พร้อมทบทวนวารสาร

สุนิสา ไทยจินดา, ณรงค์เดช โฆษิตพันธวงศ์

การศึกษานี้ได้รายงานผู้ป่วย 7 ราย ที่มีการติดเชื้อรุนแรง จนเกิดการอักเสบเน่าตาย ของผิวหนัง และเนื้อเยื่ออ่อนอย่างเฉียบพลัน ร่วมกับภาวะเลือดเป็นพิษ ในผู้ป่วยที่โรงพยาบาลหาดใหญ่ ในช่วงระหว่างเดือน มกราคม พ.ศ. 2546 ถึงเดือน มกราคม พ.ศ. 2550 อายุเฉลี่ย 50.0 $\pm$ 11.019 ปี ในจำนวนนี้ 6 ราย เป็นผู้ป่วยชาย และส่วนใหญ่ 6 ราย ที่ มีรอยโรคที่ขา ทุกรายเริ่มด้วยอาการ ปวดท้องอย่างรุนแรง ถ่ายเหลวเป็นน้ำ ตามด้วยไข้สูง พร้อมกับมีอาการและอาการแสดงของภาวะการติดเชื้อรุนแรงในกระแสเลือดร่วมกับรอยโรคที่ผิวหนัง เริ่มจากผื่นแดง ปวด ร้อน บวม พองเป็นถุงน้ำอย่างรวดเร็วภายในระยะ 1-2 วัน โดยมักมีเลือดออกอยู่ภายในถุงน้ำ เนื้อเยื่อ และผิวหนัง เกิดการขาดเลือดและเน่าตาย 3 ราย เป็นผลมาจากการติดเชื้อ กลุ่ม Streptococcus spp. อีก 3 ราย เป็นจากเชื้อ halophilic Vibrio และ 1 ราย เป็นจากเชื้อ Aeromonas hydrophila

ได้ทบทวนวารสารเกี่ยวกับอาการและอาการแสดงทางคลินิกของโรคนี้ที่ควรตรวจวินิจฉัยได้ เชื้อที่เคยมีรายงานว่าเป็นต้นเหตุ ผลของการตรวจทางจุลพยาธิวิทยาของชิ้นเนื้อ วิธีการดูแลรักษาเบื้องต้นที่ถูกต้องและเหมาะสม เพื่อช่วยชีวิตผู้ป่วยที่มีอาการติดเชื้อรุนแรง, โรคที่มักพบร่วม หรือปัจจัยที่ก่อให้เกิดการติดเชื้อ, รวมทั้งผลแทรกซ้อนที่พบ