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Characteristics of lower extremity ulcers among patients treated at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali

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ABSTRACT

Lower extremity ulcers are one of the ulcers that are difficult to heal. This condition causes significant morbidity, mortality, costs, and reduces the quality of life. Epidemiological studies in Indonesia often focus on diabetic foot ulcers, so a general description of lower extremity ulcers is still lacking. This study aimed to determine the characteristics of lower extremity ulcers in outpatients at the Dermatology and Venereology Outpatient Polyclinic, Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali. The data were taken retrospectively from medical records from January 2018 until December 2021. A total of 15 subjects were enrolled in this study. Among the subjects, 8 (53.3%) were male and 7 (46.6%) were female. The age group of 40 yo and over dominated this study (60%). The common ulcer predilection was on the cruris (42.1%) and the wound culture results were dominated by *Staphylococcus aureus* (40%). Comorbidities were found in 7 subjects (46.7%) and the majority was hypertension (42.8%). Several subjects also had additional diagnoses at the time of the visit, including Morbus Hansen (60%), deep vein thrombosis (10%), cellulitis (10%), pyoderma gangrenosum (10%), and systemic lupus erythematosus (10%). In conclusion, the most characteristics of lower extremity ulcer patients at Prof. Dr. I.G.N.G Ngoerah General Hospital are males, age group > 40 yr, with cruris as a predilection, and hypertension as the most common comorbid.

ABSTRAK

Ulkus ekstremitas bawah merupakan salah satu ulkus yang sulit sembuh. Kondisi ini menyebabkan morbiditas, mortalitas, dan beban biaya yang cukup berat serta pernurunan kualitas hidup. Penelitian epidemiologi di Indonesia seringkali fokus pada ulkus kaki diabetik sehingga gambaran ulkus ekstremitas bawah umumnya masih kurang. Penelitian ini bertujuan untuk mengkaji karakteristik ulkus ekstremitas bawah pasien rawat jalan di Poliklinik Kulit dan Kelamin, Rumah Sakit Umum Prof. Dr. I.G.N.G Ngoerah, Denpasar, Bali. Data diambil secara retrospektif dari rekam medis dari Januari 2018 hingga Desember 2021. Sebanyak 15 subjek terlibat dalam penelitian ini yaitu 8 (53,3%) subjek laki-laki dan 7 (46,6%) perempuan dengan kelompok usia di atas 40 tahun paling banyak (60%). Predileksi ulkus tersering pada kruris (42,1%) dan hasil kultur luka didominasi oleh *Staphylococcus aureus* (40%). Kondisi komorbid dijumpai pada 7 subjek (46,7%) dengan mayoritas adalah hipertensi (42,8%). Beberapa subjek memiliki diagnosis tambahan pada saat kunjungan, antara lain Morbus Hansen (60%), *deep vein thrombosis* (10%), selulitis (10%), pioderma gangrenosum (10%), dan lupus eritematosus sistemik (10%). Simpulan, karakteristik pasien ulkus ekstremitas bawah di Rumah Sakit Umum Prof. Dr. I.G.N.G Ngoerah didominasi oleh laki-laki, usia 40 tahun ke atas, predileksi dominan pada kruris, dengan hipertensi sebagai komorbid paling sering.

Keywords:
lower extremity, retrospective, ulcers

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INTRODUCTION

Ulcers are described as wounds that occur on the skin that can cause loss of epidermal tissue, dermis, and even subcutaneous fat.[1] The incidence of ulcers increases with age and is exacerbated by atherosclerosis risk factors such as smoking, obesity, and diabetes.[2] If the ulcer does not improve within three months after receiving appropriate therapy or does not completely heal within 12 months, it is called a chronic ulcer.[3]

Lower extremity ulcers are one of the ulcers that are difficult to heal.[4] Its prevalence varies widely between countries and follows trends in existing risk factors.[3] There are at least 49 million cases of lower extremity ulcers worldwide each year, with a cumulative lifetime risk of 1.0% to 1.8%.[2] In Switzerland and India, cases of chronic lower extremity ulcers range from 0.2 to 4.5 per 1000 individuals. Western Australia reported a lower extremity ulcer prevalence of 0.11% and incidence varied between 393 to 839 per 100,000 individuals in New Zealand.[5] A retrospective study conducted by Wardhana *et al.*[6] in Sanglah General Hospital, Denpasar from 2015 to 2018, 31 cases of leg ulcer were reported. Lower extremity ulcers greatly have an impact on morbidity, quality of life and mortality. Leg ulcers also can produce several complication, mostly infection, and severe pain. The infection is caused by a germ invasion which then proliferates and causes several clinical signs such as redness or swelling outside the ulcer, warm in palpation, and increases the sensation of pain or fever. If the infection lasts a long time, the tissue can experience gangrene which has high risk of amputation.[7] Therefore, the available of the lower extremity ulcers incident data is important for health facilities in order to increase attention to the prevention and screening processes of patients with injuries to lower extremity.[2]

Epidemiological studies of lower extremity ulcers in Indonesia often focus on diabetic foot ulcers, therefore a general description of lower extremity ulcers is still lacking. This study was conducted to determine the prevalence and characteristics of patients with extremity ulcers who visited the Dermatology and Venereology Outpatient Polyclinic at Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali. The information obtained from this study is expected to be usefull in the management of the lower extremity ulcers.

MATERIAL AND METHODS

Subject and design of study

This was an observational descriptive study conducted at Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali. All lower extremity ulcer patients who visited the Dermatology and Venereology Outpatient Polyclinic at Prof. Dr. I.G.N.G Ngoerah General Hospital from January 2018 to December 2021 were involved in this study.

Protocol

During the period of January 2018 to December 2021, 100 patients were recruited in this study. Furthermore, all patients were selected according to the inclusion and exclusion criteria. The inclusion criteria were the patient was diagnosed with an ulcer in their lower extremity, and was willing to participate in this study. Patients who were incomplete data were excludet from this study. Demographic data of patients from medical record such as age, gender, ulcer predilection, culture results, therapy, comorbid conditions, and additional were collected and recorded. Protocol of the study was approved by the Research Ethics Committee, the Faculty of Medicine, Universitas Udayana (671/UN14.2.2.VII.14/LT/2022).

Statistical analysis

Data were presented as frequency or percentage and analysed by using SPSS software version 20.

RESULTS

Patient characteristics

Fifteen subjects who met the inclusion and excluson criteria were enrolled in this study. Most of the lower extremity ulcer patients were males (53.3%) and mostly aged between 41 to 60 yr. Only two pstients aged <21 yr (TABLE 1).

Each subject might have more than one ulcer predilection, but most of them had ulcers on the lower leg (42.1%) and on the foot (26.3%). Details of ulcer predilection are presented in TABLE 2.

In this study only 8 subjects (53.3%) und erwent culture. The culture results were *Staphylococcus aureus* (20%), *Enterobacter aerogenes* (20%), *Citrobacter koseri* (10%), *Achromobacter denitrificans* (10%), *Klebsiella oxytoca* (10%), *Klebsiella pneumoniae sp.* (20%), and *Methycillin resistant Staphylococcus aureus* (MRSA) (10%) (TABLE 3). Two pathogens were found in two subjects, *S. aureus* and *K. oxytoca* were found in systemic lupus erythematosus (SLE) patient, and *E. aerogenes* and *C. koseri* were found in Morbus Hansen patient. MRSA was obtained in subject with HIV as comorbid.

Not all cultures as causative agents but are also considered as colonization. *Enterobacter aerogenes*, one of the culture results considered as colonization in Morbus Hansen patient. About 46.7% of patients were treated with oral antibiotics with the most common antibiotic was cefadroxil (TABLE 3). Ciprofloxacin was given to subjects with *E. aerogenes* and *A. denitrificans* culture, and one subject with *K. pneumoniae ssp* culture. Clindamycin was given to the patient with MRSA culture who had previously been given cefadroxil. The most topical ulcer treatment (46.7%) was 0.9% NaCl compresses. The other topical combination of 0.9% NaCl with a topical antibiotic (33.3%) and platelet-rich fibrin (6.7%) and 13.3% wound management by the surgeon (TABLE 3).

Comorbid conditions were only found in 7 patients (46.7%) and the majority were hypertension (42.8%). Several patients also had additional diagnoses at the time of the visit, including Morbus Hansen (60%), deep vein thrombosis (10%), cellulitis (10%), pyoderma gangrenosum (10%), and systemic lupus erythematosus/SLE (10%) (TABLE 4)

TABLE 1. Characteristics of subject

Variable	n (%)
Gender	
• Male	8 (53.3)
• Female	7 (46.6)
Age (yr)	
• 0 – 20	2 (13.3)
• 21 – 40	4 (26.7)
• 41 - 60	5 (33.3)
• >60	4 (26.7)

TABLE 2. Ulcer predilection in subjects

Ulcer predilection	n (%)
Lower leg	8 (42.1)
Foot	5 (26.3)
Lateral and medial malleolus	2 (10.5)
Toes	2 (10.5)
Thigh	2 (10.5)

TABLE 3. Culture and subjects therapy

Variable	n (%)
Wound culture	
• S. aureus	2 (20)
• E. aerogenes	2 (20)
• C. koseri	1 (10)
• A. denitrificans	1 (10)
• K. oxytoca	1 (10)
• K. pneumoniae sp	2 (20)
• Methicillin-resistant S. aureus	1 (10)
Therapy	
• Did not receive oral antibiotics	8 (53.3)
• Oral antibiotics	7 (46.7)
• Cefadroxil	4 (57.1)
• Ciprofloxacin	3 (42.8)
• Clindamycin	1 (14.3)
• Ulcer treatment	
• Compress NaCl 0.9%	7 (46.7)
• Compress NaCl 0.9% and topical antibiotic	5 (33.3)
• Compress NaCl 0.9% and PRF	1 (6.7)
• Wound care by the surgeon	2 (13.3)

TABLE 4. Additional diagnosis of subjects

Variable	n (%)
Comorbid	
• Hypertension	3 (50)
• Diabetes mellitus	1 (16.7)
• CHF	1 (16.7)
• HIV	1 (16.7)
Additional diagnosis	
• MH	6 (60)
• DVT	1 (10)
• Cellulitis	1 (10)
• Pioderma gangrenosum	1 (10)
• SLE	1 (10)

CHF: congestive heart failure; HIV: human immunodeficiency virus; MH: Morbus Hansen; DVT: deep vein thrombosis; SLE: systemic lupus erythematosus

DISCUSSION

Lower extremity ulcers are often a disease symptom, therefore knowing the underlying disease is important in providing appropriate management.[7] Many factors can lead to lower extremity ulcers that can be divided into two categories i.e. internal and external risk factors.[8] The internal risk factors include previous leg injury, employment, extended standing, and sitting behaviors that contribute to venous illness, friction, dampness, and shear force are all extrinsic variables that can cause lower extremity ulcers. While the internal risk factors include genetics, advanced age, obesity, deep venous thrombosis, phlebitis, pregnancy, estrogen levels, immobility, cognitive deficiency, chronic disease (e.g., diabetes mellitus), poor diet, steroid usage, and aging.[8,9] Meanwhile the primary risk factors for venous ulcers are older age, obesity, previous leg injuries, deep venous thrombosis, and phlebitis.[1] The common etiologies are venous ulcer, venous arteriosum, diabetic, pressure ulcer, and a combination of venosum and arteriosum. Ulcers could have several etiologies thus creating challenges in their diagnosis and management.[10] It is important to optimize the treatment to reduce morbidity and mortality.[1]

Although lower extremity ulcers are more common in the elderly, approximately 22% of cases develop ulcers for the first time at 40 yr, and 13% before 30 yr.[10] Therefore, their ability to work and social activities become hampered. It was reported that a similar matter where the annual prevalence only ranged from 0.18 to 2.1% but increased to 5% in the elderly population.[11] The increase in lower extremity ulcer cases was also found in this study. The elderly are at high risk of experiencing chronic ulcers due to various changes related to the aging process, cardiovascular disease, diabetes, impaired mobility, incontinence, low body weight, poor nutritional status, and cognitive impairment. Intrinsic changes in the wound healing process also involve the age factor, shifts in the body's inflammatory response, low extracellular matrix and growth factors, inhibition of epithelialization, and decreased angiogenic activity. This contributes to the delay in wound healing in the elderly.[12]

Lower extremity ulcers are a rare case in the pediatric group. This is due to better healing ability and a lower frequency of venous and arterial diseases. In general, the causes of lower extremity ulcers in the pediatric group more varied, but in adults, it is dominated by vascular disorders. In pediatric cases, ulcers that occur in vascular disorders are often only found in cases of malignancy or malformation.[13] In this study, the youngest age was 12 years with SLE as comorbid.

Systemic lupus erythematosus is an autoimmune inflammatory disease which can simultaneously damage the integrity of bones, joints, muscles, kidneys, and skin. Lower extremity ulcers are one of the manifestations on the skin. Vasculitis, antiphospholipid antibodies, gangrenous pyoderma, or cutaneous calcinosis can caused ulcers in SLE case.[14] Cutaneous vasculitis is the most common type of vasculitis and is reported to occur in 17-28% of SLE patients. High levels of anti-Ro and anti-phospholipids, as well as positive cryoglobulin results, are the main risk factors for cutaneous lupus vasculitis.[15] On the other hand, calcinosis is a complication characterized by calcium deposition in the soft tissues, especially to trauma, infection, or inflammation. Deposits of calcium salts will inhibit ulcer healing.[14]

Most of the subjects in this study had comorbid hypertension (42.8%). Hypertension is often associated with ulcer arteriosum. These ulcers may involve the traumatized distal foot area

as well as the anterior part of the leg due to decreased arterial blood flow and tissue perfusion.[1,16] Arterial or arteriolar occlusion will cause ischemia of the skin and subcutaneous tissue resulting in ulcers. Peripheral vascular disease due to atherosclerosis, diabetes with micro and macrovascular disorders, and vasculitis can also contribute to this process. The emergence of ulcers often occurs quickly and there is deep enough tissue destruction. The ulcer will appear as a "punched out" lesion with well-defined margins, a pale base, non-granulating, and necrotic.[1]

Heart failure is a risk factor for stasis ulcers. Increased leg edema is an important mechanism associated with hypoxemia occurs in patients with isolated left heart failure. Augey *et al*.[17] explained that stasis ulcers had a strong correlation with heart failure. Conversely, heart failure is also significantly associated with bilateral ulcers.

Physician treating patients with HIV infection are faced with a spectrum of skin complaints which is different from that seen before antiretroviral drugs became widely used. Cutaneous infections caused by MRSA are a growing cause of morbidity and mortality although overall there appears to be improved immune function with anti retroviral therapy.[18]

Several subjects also had additional diagnoses at the time of the visit, including Morbus Hansen (60%), DVT (10%), cellulitis (10%), pyoderma gangrenosum (10%), and SLE (10%). Patients with borderline tuberculoid leprosy have a higher risk of developing chronic ulcers, followed by individuals with the lepromatous and borderline lepromatous forms.[19] Ulcers are uncommon feature in leprosy patients, except during leprosy reactions, Lucio's phenomenon, or occur secondary to neuropathy.[20] The mechanism is the invasion of bacilli directly into the walls of blood vessels and endothelium. It determines the local granulomatous reaction of each type of tuberculoid, vasculitis, skin necrosis, and ulceration.[19]

Walker *et al*.[21] explained that patients who experience deep vein thrombosis have an increased risk of lower extremity ulcers up to three times. This is supported by the findings that 24% of asymptomatic venous thrombosis patients develop chronic venous insufficiency two to four years after surgery.[21] Mouawad uses the term post-thrombotic syndrome for a chronic condition that occurs in 50% of deep vein thrombosis patients and the clinical manifestation includes venous ulcers.[22]

Patients with lower extremity ulcers are at risk of developing cellulitis. Cellulitis occurs after a bacterial infection of the skin. Not only the surface of the skin, but this infection can also spread to the subcutaneous tissue, spread through the lymph nodes and blood vessels. Cellulitis that occurs secondary to lower extremity ulcers is generally caused by pathogenic *Streptococci*, *Staphylococci*, *Pseudomonas spp*., and *Bacteriodes spp*.[23]

Pyoderma gangrenosum is a destructive inflammatory condition characterized by painful ulcers and neutrophilic infiltration of the dermis. Although it often occurs in areas of venous insufficiency, clinicians must be able to differentiate it because PG requires immunosuppressant therapy. Pyoderma gangrenosum lesions have major criteria, necrolytic ulcers on the skin which are accompanied by pain, have rapid progression, irregular edges, and purplish in color, and the other causes of skin ulcers have been excluded.[24]

Ulcer predilection can lead to a diagnosis. This study was dominated by leg ulcers (42.1%) followed by pedis ulcers (26.3%). Agale[1] described that venous ulcers generally occur over the medial or lateral malleolus.[1] On the other hand, arteriosum ulcer can appear

unilaterally or bilaterally and tends to involve the big toes, feet as well as heels.[1,10,25] Neuropathic ulcers are often found on the plantar pedis or at pressure points. Patients with limited mobility or obesity may develop ulcers in the gaiter area due to venous hypertension resulting from inadequate pumping of the calf muscles.[1] Diabetic ulcers are induced by peripheral neuropathy as well as peripheral arterial disease. Approximately 50% of cases occur in the toes and between the toes, the rest are in the forefoot, midfoot, or heel.[10]

The prevalence of infection in chronic ulcers ranges from 22 to 27%.[26] The infection will slow wound healing and increase complications and mortality. A culture examination can be conducted to provide the most appropriate antibiotic.[26] Patient aged > 65 yr, ulcer duration >12 mo, and ulcerated area > 8.25 cm^2 are independent predictors of positive wound culture.[27] It should be remembered that ulcer contaminants can come from three main sources: 1) the environment i.e. airborne or exogenous microorganisms from traumatic injury, 2) adjacent skin, and 3) endogenous sources involving mucous membranes.[28]

Infection of lower extremity ulcers can be caused either by Gram-positive or Gram-negative bacteria. The most common organism isolated were *S. aureus*, *P. aeruginosa*, *E. faecalis*, *K. pneumoniae*, and *E. coli*.[29] In this study, *S. aureus, E. aerogenes,* and *K. pneumoniae ssp* predominated and was found in 20% of the subjects. Gjødsbøl *et al*.[28] also reported that *S. aureus* often isolated from chronic foot ulcers. Data indicated that this pathogen can be present in 20 to 50% of wound cultures.[30]

Enterobacter aerogenes is one of the normal flora in human digestive tract which is a nosocomial pathogen and a common cause of iatrogenic bacteremia. Although community-acquired infections are occasionally encountered, nosocomial infections are the most common. Patients who are most susceptible to infection are those who stay in the hospital, especially in the intensive care unit for a long time. Other major risk factors are prior use of antimicrobial agents, co-morbid malignancy (especially hemopoietic and solid organ malignancies), hepatobiliary disease, upper gastrointestinal ulcers, diabetes mellitus, chronic renal failure as well as immunosuppression.[31] Donastin also found that 18% of his research samples were infected with *E. aerogenes*.[32]

Achromobacter is low-virulence Gram-negative bacilli and has rarely been reported to cause clinically significant skin infections. However, recently it has emerged as an infectious agent in both immunocompromised and immunocompetent populations.[33] *Achromobacter* sp isolates are resistant to first and second-generation cephalosporins, aminoglycosides, and narrow-spectrum penicillins. These bacteria are generally susceptible to sulfonamides, carbapenems, and the broad-spectrum penicillins of third-generation cephalosporins, and are especially susceptible to fluoroquinolones.[34] In line with this, the subjects in this study received ciprofloxacin.

Klebsiella oxytoca commonly colonizes the soft tissues of the respiratory and gastrointestinal tract in patients with severe underlying disease and is rarely associated with lower extremity ulcers, particularly diabetic ulcers.[35] A previous study in Nigeria reported that this pathogen is found in 13% of cases of chronic lower extremity ulcers and was sensitive to third-generation cephalosporins and fluoroquinolones.[36] In this study we found 10% of cases *K. oxytoca* isolate.

Antibiotic therapy can be given to all adult patients with lower extremity ulcers who have clinical signs of infection. It is determined by the degree of severity

of symptoms or signs of infection, a person's risk of complications, and also a history of previous use of antibiotics.[37] The most sensitive antibiotics for Gram-positive bacteria in a study at a hospital in Surabaya on diabetic foot ulcers were amikacin, teicoplanin, and oxacillin while the most resistant was amoxicillin and ampicillin. The most sensitive antibiotic for Gram-negative bacteria in this study was meropenem and the most resistant for Gram-negative bacteria were ciprofloxacin and trimethoprim-sulfamethoxazole.[32] The sensitivity test or distribution map of pathogens in each health center needs to be reviewed when giving antibiotics because there is a possibility of different sensitivity patterns. An antibiotic sensitivity test was also carried out on some of these subjects in this study. However, it can not be concluded the antibiotic sensitivity and resistance pattern due to insufficient samples.

CONCLUSION

This study find that patients with lower extremity ulcers at the Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali commonly affects males patients with age group >40 yr. In addition, hypertension is the most comoon comorbid.

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